Executive dysfunction or slowed information-processing speed in Parkinson's disease?

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Contents

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Abstract

Recent evidence has shown that PD patients can exhibit impaired performance in tests such as verbal fluency that are sensitive to frontal lobe dysfunction. Two accounts have been proposed to explain the observed PD impairments; slowed information-processing speed (bradyphrenia), or specific executive dysfunction. The current study aimed to explore verbal fluency performance in PD patients in an effort to determine which account is most pertinent. Eight PD patients were compared to eight controls on experimental measures of verbal fluency and numerical information-processing (NIP), as well as background neuropsychological tests. In addition to word output measures, patterns of clustering (generating words within categories) and switching (shifting between categories) were assessed in verbal fluency tasks. A novel paradigm was employed that manipulated the executive load of fluency tasks by constraining the number of syllables. In addition, a novel measure of information-processing speed was employed that had three executive load levels. PD patients produced fewer words than controls in almost all the fluency tasks. The clustering and switching analyses revealed that patients had disproportionately slower switching times than controls in one of the letter conditions. The PD group was impaired relative to controls in the both measures of syllabic fluency. The NIP task revealed that PD patients were significantly slower than controls in the high executive demand condition only. It is argued that the observed pattern of results support the presence of a specific executive impairment in PD rather than general cognitive slowing. Furthermore, the techniques used in the current study show potential for development in this line of investigation.

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1. Introduction

1.1 Parkinson's Disease

Parkinson's disease (PD) is neurodegenerative disorder that is characterised primarily by movement problems including muscular rigidity, slowed movement (bradykinesia), and resting tremor (Lysia & Forno, 1996). The disorder is caused by depleted subcortical dopamine levels which disrupt motor circuitry and manifest in the observed movement abnormalities. In addition to motor problems, it is becoming increasingly apparent that PD patients also experience deficits in cognitive functioning. Impairments have been consistently reported on tasks requiring working memory, attention, and executive functioning (Cooper, Sagar, Jordan, Harvey & Suilivan, 1991; Zgaljardic, Borod, Foldi & Mattis, 2003). PD can be caused by severe cerebral trauma, encephalitis, drug abuse and carbon monoxide poisoning, amongst other environmental factors. Most cases however, are idiopathic, and as such occur in the absence of any other fundamental neurological problem (Pearce, 1978). The prevalence rate of PD in the UK is around 1 in 500 (0.2% of the population), with the vast majority of those diagnosed being over the age of 50 (Parkinson's disease society, 2009). The ageing populations of western countries mean that comprehensive understanding and effective management of this disorder is paramount.

1.2 Neuropathology of PD

The fundamental neuropathological feature of PD is progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta; a discrete structure within the basal ganglia that is responsible for the production of the neurotransmitter dopamine (Lysia & Forno, 1996). Depleted dopamine levels severely disrupt the nigro-striatal pathway, which in turn disrupts the frontostriatal circuitry that mediates the transmission of neural signals between motor cortex and the basal ganglia. This subcortical-cortical circuitry is responsible for control of voluntary movements, and disruption results in a Parkinsonian movement profile. However, subcortical-cortical circuitry is not confined to motor control; dorsomedial projections from the substantia nigra lead to the caudate nucleus (Owen, 2004). Studies of non-human primates have shown that the caudate nucleus is heavily connected to different areas of prefrontal cortex and suggest that this

structure is the major link between the basal ganglia and frontal regions (Yeterian and Pandya, 1991). Indeed, it has been shown that there are 3 distinct circuits that link the substantia nigra to frontal areas via the striatum and the thalamus; these are known as *complex* frontostriatal circuits (Alexander, Crutcher & DeLong, 1990). These complex frontostriatal circuits have been identified in higher primates, and their existence in humans is supported by neuroimaging studies in healthy adult participants (Cools, Stefanova, Barker, Robbins & Owen, 2002b). Projections originating in orbitofrontal prefrontal cortex (OFC) are connected to ventromedial portions of the caudate nucleus, composing the *lateral orbitofrontal circuit*. Projections originating in anterior cingulate cortex (ACC) are connected to ventral (limbic) striatum, composing the *anterior cingulate circuit*. Projections originating in areas of dorsolateral prefrontal cortex (DLPFC) are connected to dorsolateral portions of the caudate nucleus, composing the *dorsolateral prefrontal circuit* (Cummings, 1993). The DLPFC is implicated in working memory and executive functions such as strategy formation, set-shifting, planning, and attention (Stuss & Benson, 1986). OFC mediates the control of mood and emotion, and reward-based learning, whereas ACC is involved in attentional monitoring and inhibition (see Zgaljardic *et al.,* 2003 for a review). It follows that the cognitive processes underpinned by these cortical regions will be affected by disruption of the related frontostriatal circuitry. Patients with PD have highly depleted dopamine levels within the caudate nucleus, especially the dorsolateral portion (Owen, 2004). This pathology will disrupt the normal flow of information between the basal ganglia, thalamus and the target frontal regions. Thus, frontal dysfunction in PD may be caused *indirectly* by the disruption of the *connections* between cortical and subcortical structures (Zgaljardic *et al.,* 2003).

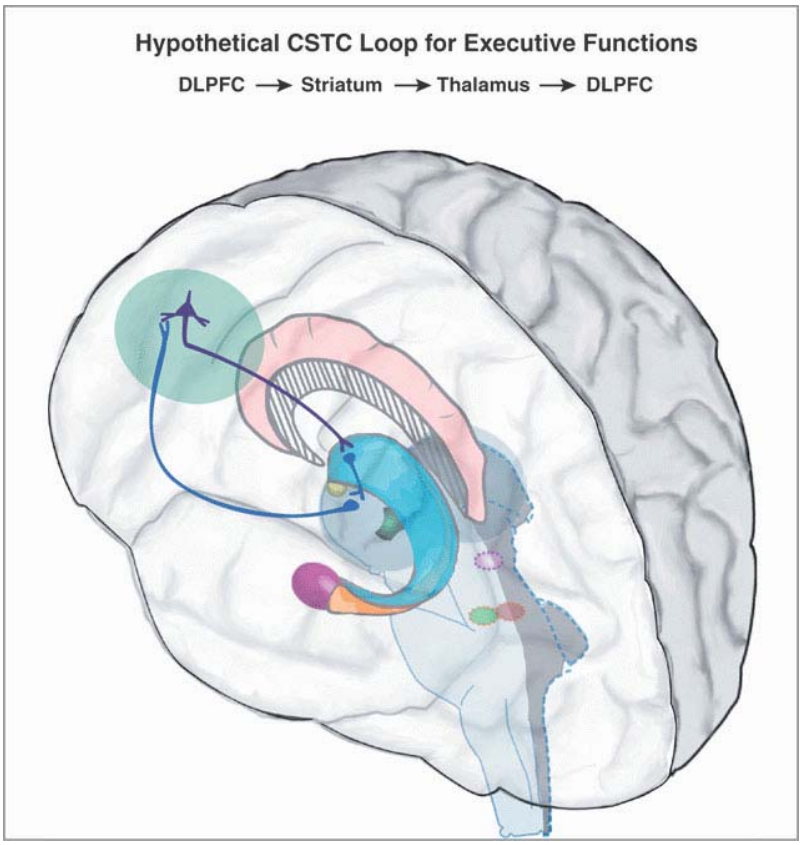


Fig. 1. Fronto-striatal circuitry to dorsolateral prefrontal cortex (http://stahlonline.cambridge.org)

However, there is also a *direct* dopaminergic pathway from the subcortical ventral tegmental area (VTA) to prefrontal cortical areas, known as the mesocortical pathway (Mattay *et al*, 2002). It has been suggested that this pathway is important for the efficiency of frontal processing (Goldman-Rakic, 1998), and as such, dopamine depletion in mesocortical circuits may also contribute to the executive impairments observed in PD (Mattay *et al*, 2002). However, as Owen (2004) notes, dopamine depletion in the VTA is significantly less – typically 50% – than dopamine depletion in the SN of PD patients, suggesting that the mesocortical pathway may have less impact on cognitive functioning than the frontostriatal pathways. None-the-less, the mesocortical pathway represents a route between subcortical and frontal areas that is mediated directly by dopamine, and as such its influence on cognitive functions may be significant. Degeneration of nerve cells within the substantia nigra (SN) is not the only neuropathological symptom of PD; cellular degeneration is also observed in the structures that produce norepiniephrine

(locus ceruleus) and acetylecholine (nucleus basalis of the Meynert), implicating these neurotransmitters in PD sequelae (Rowe *et al.,* 2008). Indeed, pharmacological studies have shown that blocking cholinergic uptake in PD patients can result in learning impairments and executive dysfunction (Dubois and Pillon, 1997). In addition, degenerartion of the SN is often, but not always, accompanied by the presence of Lewy bodies, although the exact nature and affect of these structures is yet to be resolved. However, the dramatic loss of dopaminergic neurons in the SN, and the subsequent fundamental disruption of subcortical pathways to the frontal lobes, means that dopamine deficiency remains the most likely candidate for the cognitive impairments observed in PD (Dubois & Pillon, 1997).

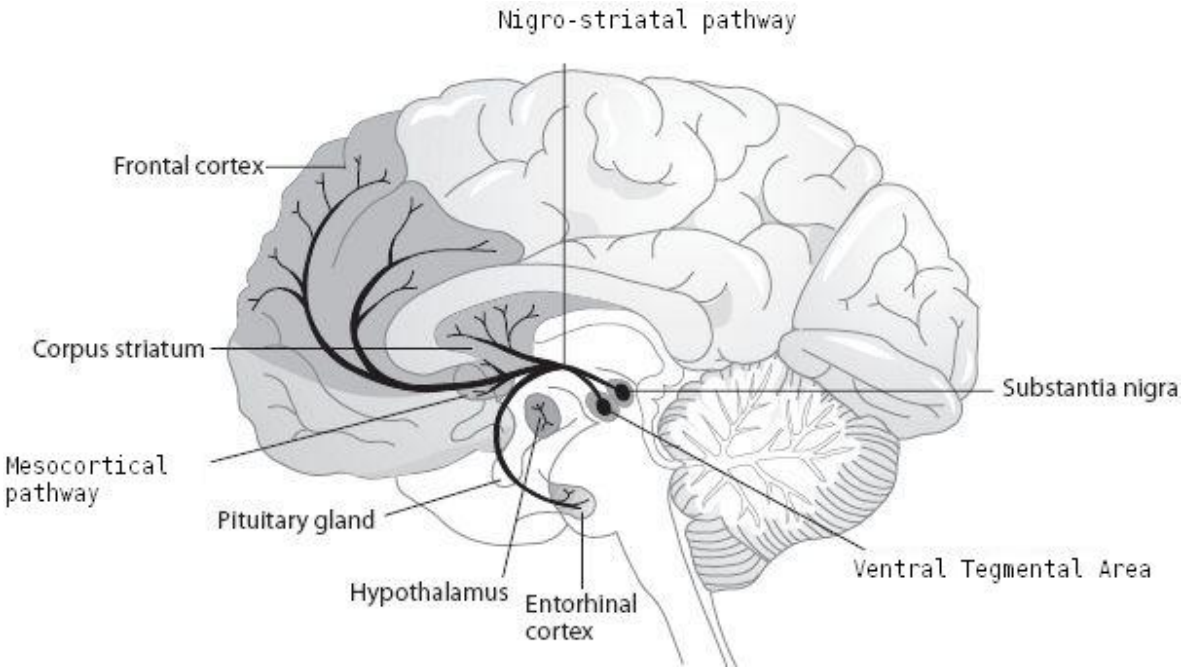


Fig. 2. Dopamine pathways from the Ventral Tegmental Area and Substantia nigra (http://content.answers.com)

1.3 Cognitive performance in PD

Although Parkinson's (1817) first account of the disorder claimed that impairments were restricted to motor functioning, recent studies have provided a strong body of evidence to show that in fact, cognitive dysfunction is a common occurrence in PD. Deficits have been reported in non-demented PD patients in a wide spectrum of cognitive processes

including: working memory (Cooper *et al.*, 1991), visuospatial working memory (Morris, Downes, Sahakian, Evenden, Heald & Robbins, 1988), explicit memory (Dujardin, Defebvre, Grunberg, Becquet & Destee, 2001), language (Skeel, Crosson, Nadeau, et al., 2001), attention (Ridenour & Dean, 1999), mood (Hantz, Caradoc, Caradoc *et al.*, 1994), and executive functions (Dubois & Pillon, 1997). Moreover, although the cognitive impairments in PD are often described as subtle, recent studies have demonstrated that the impairments translate into difficulties in everyday mental functioning, and hence cause a detrimental affect to quality of life (Poliakoff & Smith-Spark, 2008). However, there appears to be a lot of variation in the prevalence of cognitive impairments reported in the PD literature. Troster (2006) suggested that around 40% of PD sufferers will present with some form of cognitive impairment, however some studies report deficits in up to 93% of patients (Jacobs, Stern & Mayeux, 2000). Other researchers have postulated that there are multiple subgroups of PD, each with their own discrete motor and cognitive symptoms (Graham & Sagar, 1999). A study by Lewis, Foltynie, Blackwell, Robbins, Owen and Barker (2005) reported a cohort of PD patients with 4 distinct subgroups; patients with early disease onset, tremor dominant patients, non-tremor dominant patients with significant levels of cognitive impairment and mild depression, and patients with no apparent cognitive deficits despite rapidly progressing motor symptoms. However, Owen (2004) maintains that the most useful division in PD is between those patients who experience executive dysfunction, and those who do not. In addition to the issue of heterogeneity with PD, it has also been shown that between 30% and 50% of PD patients develop dementia (Jacobs, Stern & Mayeux, 2000). This prompts further subdivision of the disorder as demented PD patients can develop a variety of cognitive impairments that cannot be attributed solely to PD pathology (Woods & Troster, 2003). None-the-less, there is an emerging consensus that a significant proportion of *non-demented* PD patients experience specific cognitive impairments (Zgaljardic et al., 2003; Owen, 2004), and as such, the current study will focus on the nature and source of deficits in this population.

The broad nature of the cognitive problems observed in PD has lead some researchers to explain the impairments in terms of general cognitive slowing, or bradyphrenia (Naville, 1922; Wilson, Kaszniak, Klawans & Garron, 1980). Bradyphrenia has been defined in a

variety of terms including: slowed mental processing due to disrupted concentration and apathy (Rogers, 1986), impairments in attention and vigilance (Mayeux, Stern, Sano, Cote & Williams, 1987), and slowed mentation in the presence of *preserved* attentional capacities (Taylor, Saint-Cyr & Lang, 1986). More recently however, the phenomenon has been cognitively conceptualised as slowed information-processing speed (Revonsuo, Portin, Koivikko, Rinne & Rinne, 1993). This deficit is thought to reflect a secondary pathology associated with the same disrupted dopaminergic pathways of the basal ganglia that cause motor slowing (bradykinesia) (Rafal, Posner, Walker & Friedrich, 1984).

Evidence for the information-processing account comes from experiments that are devised to require an increasing cognitive load coupled with a constant motor response. Wilson *et al.* (1980) employed the Sternberg (1975) paradigm which is designed to assess scanning speed within short-term memory, independent of motor functioning. Participants were first presented with digit strings, followed by the presentation of a single digit – the task was to decide whether or not the single digit was a component of the previous digit string. As the number of digits in each string increases (i.e. as cognitive load increases), reaction times increase incrementally. However, the reaction times of PD patients increased significantly more than that of controls, suggesting that their "thinking times" were disproportionately slowed as the amount of information increased. The authors concluded that PD patients could not scan their memory of digits as efficiently as controls due to a deficit in information-processing speed. Similar results have been found using a digit-symbol substitution task, although the cognitive component of the task was only significantly longer in those PD patients who had CT scan abnormalities (Rogers, Lees, Smith, Trimble & Stern, 1987). In contrast to these studies, Rafal et al. (1984) found no evidence of slowed memory scanning using the same paradigm as Wilson et al. (1980), casting doubt on whether cognitive slowing is really evident in PD.

To explain the slowed information-processing speed account of PD impairments it is necessary to understand exactly what is meant by *information processing*. The concept can be defined as the processing of sensory information that requires an end-point motor response (Vlaar & Wade, 2003). Revonsuo *et al.* (1993) postulated that there were three

distinct stages in information processing; *automatic visual processing* within the perceptual system, *controlled effortful processing* requiring decision-making within working memory, and *motor programming* (usually automatic, but may require conscious effort in PD). The authors devised separate reaction time tasks to investigate PD performance in each stage of information processing. A visual recognition task assessed automatic processing, a subtraction task requiring basic mental arithmetic assessed controlled processing, and simple stimulus-response tasks assessed motor programming. The results from Revonsuo *et al's* (1993) study indicated that PD patients were slower than controls in the automatic processing and controlled processing tasks, but not the motor programming task. The impairments in the controlled processing stage were thought to reflect a central processing deficit due to weakened working memory capacity and attentional resources resulting in slowed "central processing".

A major critique of these studies comes from the possible confounding effects of bradykinesia on reaction time scores. Reaction time studies rely on the assumption that time differences in tasks requiring different cognitive components with the same motor response are an exact reflection of cognitive processing. However, this is not necessarily the case, particularly in the light of evidence that suggests that there can be an interaction between cognitive and motor processing (Georgopoulos, 2000). To address this issue, a study by Shipley, Deary, Tan, Christie and Starr (2001) employed a temporal order discrimination task which required participants to report the temporal sequence of 4 letters that are presented within very short time frames. Different conditions employ decreasing time frames for each letter (starting at 700ms and decreasing to 100ms). The task is therefore a measure of information-processing speed, in the absence of a reaction time constraint. Shipley *et al.* (2001) reported that PD patients got fewer sequences correct than controls in the time frame durations of less than 500ms, suggesting that PD performance is compromised in tasks requiring fast information-processing. The result was accounted for in terms of inefficient information processing due to deficits in encoding or retrieval of the presented stimuli.

Studies addressing information-processing speed in PD show a high degree of variation in results; this probably reflects the ambiguity surrounding the concepts of bradyphrenia and information-processing speed. The fundamental components of information-processing are not consistent from task to task; some require only automatic processes (e.g. visual recognition – Shipley *et al.,* 2001), whereas some require consciously controlled processes (e.g. decision making – Wilson *et al*., 1980; Revonsuo *et al.*, 1993). As such, it appears to be very difficult to separate the concept of information-processing from the cognitive processes that pertain to executive functioning and working memory.

Throughout the literature, the most commonly reported impairments in PD are those of executive functioning and working memory (Dubois & Pillon, 1997). Working memory refers to a short-term sensory store in which visual and/or auditory information can be represented, maintained and manipulated (Baddeley and Logie, 1999). PD patients have been shown to have specific deficits in verbal and visuospatial working memory (Gabrielli, Singh, Stebbins & Goetz, 1996; Morris *et al.,* 1988), although there are other studies that claim working memory remains intact in PD (Bradley, Welch & Dick, 1989). Executive functioning is the umbrella term for high order cognitive processes such as planning, attention, monitoring, problem solving, strategy formation, inhibition, and set shifting - processes that are required in challenging and novel situations to achieve goal-directed behaviour (Zgaljardic *et al.,* 2003). PD patients consistently exhibit impaired performance in the following tasks designed to target executive functions;

1). Wisconsin Card Sort Test (Taylor, Saint-Cyr & Lang, 1986) which requires set-shifting and inhibition to react to the changing rules and patterns of the card sorting task.

2). Tower of London type paradigms (Owen *et al.*, 1992; Morris *et al.*, 1988) which require problem solving, planning and strategy formation to achieve a spatial construction in the least number of moves possible.

3). Verbal fluency (Lees & Smith, 1983; Taylor, Saint-Cyr & Lang, 1986; Azuma et al., 1997) which requires generation of search strategies and the ability to switch strategy and monitor responses to produce as many words as possible beginning with a given letter.

4). Trail making tasks (Taylor, Saint-Cyr & Lang, 1986) which require set-shifting, attentional monitoring and inhibition to switch between letters and numbers when completing the trail.

5). The Stroop test (Dubois, Boller, Pillon & Agid, 1991) which requires inhibition, set-shifting and response monitoring to correctly name the colours of words printed in conflicting coloured ink.

It should be noted that many of the tasks described above also require working memory to keep in mind and manipulate the relevant goal-directed information, and so impairment in performance may reflect a combination of working memory and executive deficits. Indeed, it has been suggested that all reported PD impairments in cognitive tasks are due to an underlying executive dysfunction and working memory deficit (Della Sala, 1988; Zgaljardic *et al.,* 2003). For example, PD patients display normal learning curves and show normal levels of information loss after delays, however, they perform badly when the material to be remembered requires temporal ordering or organisation – i.e. an executive component (Taylor, Saint-Cyr & Lang, 1990). Thus, apparent deficits in episodic memory may reflect poor generation of retrieval strategies rather than a memory problem *per se*. Similarly, visuospatial performance is typically only compromised when the task requires an executive component such as set-shifting, suggesting that poor performance is independent of a pure visuospatial deficit (Raskin, Borod & Tweedy, 1992). In addition, many of the tasks designed to assess information-processing speed require information to be maintained and a judgement to be made, thus placing an additional demand on executive processes and working memory (e.g. the Sternberg paradigm; Wilson *et al.,* 1980).

The cognitive profiles of PD patients bare similarities to those patients who have suffered frontal lobe damage and experience specific frontal dysfunction – executive functions, attention and working memory are predominantly impaired (Taylor, Saint-Cyr & Lang, 1986; Owen *et al.,* 1992). Such comparisons are suggestive of frontal lobe disruption in PD patients – and in particular to the areas of cortex that mediate the observed impairments. There is a large body of behavioural, neuropsychological and neuroimaging evidence to show that the frontal lobes are modular in nature (Stuss & Benson, 1986;

Baddeley & Della Sala, 1998), and three functionally and anatomically discrete regions have been proposed to be involved in PD sequelae. Lesions to anterior cingulate cortex (ACC) typically result in apathy and attentional deficits including response initiation, sustained attention and response monitoring (Stuss *et al.,* 1998). PD patients with high levels of apathy have shown impaired performance in these attentional domains (Pluck & Brown, 2002). Orbitofrontal cortex (OFC) is generally considered to mediate emotional and social processing and damage to this area will often result in behavioural instabilities such as depression, disinhibition and obsessive-compulsive disorders (Masterman & Cummings, 1997). However, OFC may also play a role in cognitive functions such as reward-based learning. This is highlighted by gambling tasks in which patients with damage to OFC make impulsive and irrational decisions (Bechara, Damasio & Damasio, 1994). PD patients have exhibited varying levels of performance on stimulus-reward tasks tapping OFC function, depending on their level of dopamine medication (Cools *et al.,* 2001). Dorsolateral prefrontal cortex (DLPFC) is considered the most influential cortical area in executive functioning (Smith & Jonides, 1999), as it appears to coordinate processes such as memory, attention and planning to achieve goal-directed behaviour (Baddeley & Della Sala, 1998). Patients with lesions to DLPFC often present with "executive dysfunction" which is characterised by impaired performance in working memory, strategy formation and set-shifting tasks (Stuss & Benson, 1986; Shallice, 2002). Executive functions are among the most commonly reported impairments in PD patients (Owen, 2004; Zgaljardic *et al,* 2006). Furthermore, functional imaging studies have revealed that PD patients who experience executive dysfunction also show decreased activation of DLPFC (Lewis, Dove, Robbins, Barker & Owen, 2003). Thus, it would appear that the discrete areas of prefrontal cortex, with emphasis on DLPFC, are implicated in the observed cognitive impairments of PD.

A potential complication regarding the cognitive effects of PD neuropathology arises from the medication used to treat the disorder. PD is typically treated with dopamine agonists or metabolic inhibitors. Both drug types have the same overall effect of increasing the net amount of dopamine in the brain. A recent study by (Rowe *et al.,* 2008) investigated the differential effects of dopamine level on the discrete frontostriatal

circuits, and cognitive functions that they mediate. The authors found that different circuits require different levels of dopamine for optimal performance. As such, dopaminergic medication can improve some cognitive functions but impair others; the effects are dependent on a patient's baseline dopamine levels *and* the strength of their subsequent medication. These interactions may go some way to explaining the wide range of executive impairments evident in PD.

1.4 Verbal Fluency

Verbal fluency tasks are widely used methods of neuropsychological assessment. There are two main types of fluency task; phonemic (letter) and semantic (category). Phonemic fluency involves the participant being instructed to produce as many words as possible beginning with a specified letter, in a limited period of time (typically one minute). In semantic fluency tasks, the same procedure applies except that participants are instructed to produce words within a specified category (e.g. animals). Fluency tasks are typically scored by the total number of words generated, although relatively new research has suggested that this method may not be the most accurate reflection of performance (Troyer, Moscovitch & Winocur, 1997). Both versions of the task are applied commonly in clinical settings, and neuropsychological evidence suggests that each task is sensitive to a variety of cognitive disorders (Azuma, 2004). Semantic fluency is more sensitive to disorders of the temporal lobes such as Alzheimer's dementia (Hodges, Salmon & Butters, 1990), whereas phonemic fluency is more sensitive to frontal dysfunction and disruption of the fronto-striatal pathways evident in subcortical disorders (Baldo & Shimamura, 1998; Piatt, Fields, Paolo, Koller & Tröster, 1999).

Neuroimaging studies provide evidence to support the involvement of differential cortical areas in the different verbal fluency tasks. A functional Magnetic Resonance Imaging (fMRI) study by Abrahams *et al.* (2003) investigated phonemic fluency performance in older adults. The authors employed a paradigm that overcame the usual movement artifacts that arise in fMRI data when vocal responses are required. The authors reported that significant activation in the middle frontal, inferior frontal, and anterior cingulated gyri (prefrontal areas) was associated with the fluency task suggesting that phonemic

fluency is primarily mediated by the frontal lobes. Evidence from neuropsychological studies also supports the role of the frontal lobes in phonemic fluency tasks. A study by Baldo, Schwartz, Wilkins and Dronkers (2006) employed voxel-based lesion symptom mapping in stroke patients with left hemisphere lesions. The authors reported that patients with temporal lesions were associated with poor performance in semantic fluency whereas those patients with frontal lesions were associated with poor performance in phonemic fluency, supporting the postulated differentiation between the relative fluency tasks.

Phonemic verbal fluency tasks require the generation of words that are phonetically related. This is a complex task that draws on a number of discrete cognitive functions. Clearly, basic word retrieval is necessary which requires efficient access to the lexical store, and this should be investigated and controlled in the tested population (Abrahams *et al.,* 2000). However, a number of additional processes are also necessary for good performance in fluency tasks (Azuma, 2004; Abrahams *et al.,* 2000; Bittner & Crowe, 2007).

- Initiation is required to start lexical searches
- The selection of relevant lexical information requires the generation of appropriate retrieval strategies.
- Sustained attention is required to maintain task performance.
- Cognitive set-shifting is required switch between different retrieval strategies.
- Information-processing speed is required to maintain an adequate response rate.
- Working memory and inhibition are required to monitor previously generated items.

Many of these processes are recognized as executive functions as they require internally generated plans that must be continually monitored and updated (Baddeley, 1996; Troyer, Moscovitch & Winocur, 1997). In particular, phonemic fluency tasks are executively demanding as they rely solely on lexical cues to guide word production; therefore requiring the dynamic and systematic generation of different retrieval strategies, and the ability to switch between them. Poor performance in verbal fluency tasks is reflected by a number of different error types. The most common are perseverative errors (repetition of

a previously generated word), and set-shifting errors (the failure to generate, and switch between different retrieval categories). Errors of this type are indicative of poor attentional supervision and executive dysfunction. The "central executive" (Baddeley, 1996) or the analogous "Supervisory Attentional System" (SAS; Shallice, 1988) are cognitive constructs which play an important role in control of cognitive processes, especially in novel situations. Thus, a deficit in the SAS or central executive would manifest in poor performance in tasks such as verbal fluency which require novel behaviours to be initiated and place high demands on attentional control.

1.5 Fluency Performance in PD

Given the sensitivity of verbal fluency tasks to frontal lobe pathology (Crowe, 1992; Baldo & Shimamura, 1998) the tasks seems to be an appropriate method of investigation in PD populations. Indeed, there has been fairly extensive investigation of fluency performance in PD. However, the findings have been largely inconsistent. Several researchers have reported that semantic fluency performance is more affected by PD than phonemic fluency (Matison, Mayeux, Rosen & Fahn, 1982; Raskin, Sliwinski & Borod, 1992; Fama *et al.*, 1993), whilst others have found the opposite relationship with phonemic fluency reported as the main impairment (Bayles, Trosset, Tomoeda, Montgomery & Wilson, 1993; Flowers, Robertson & Sheridan, 1995; Azuma et al., 1997). Moreover, several studies have reported intact phonemic fluency (e.g. Auriacombe *et al.*, 1993), whereas other studies have found deficits in both fluency tasks (Gurd & Ward, 1989).

The inconsistencies in the fluency literature may be a reflection of the heterogeneous nature of PD. For example, many of the earlier studies mentioned above (e.g. Matison *et al.*, 1982; Flowers, Robertson & Sheridan, 1995) did not administer background tests of intelligence or dementia screening, and therefore some of the patients in the cohort may have been demented. Disease severity may also be a cause of variation in the studies; Matison et al, (1982) reported that semantic fluency impairments correlated with disease severity and bradykinesia in their PD population. Furthermore, Hanley, Dewick, Davies, Playfer and Turnbull, (1990) showed that intelligence and age play an influential role in

verbal fluency performance; their initial results showed that PD patients were impaired on measure of phonemic and semantic fluency, however, the impairments ceased to be significant when age and verbal ability were taken into account. A subsequent study by Bayles *et al.* (1993) directly compared demented and non-demented PD patients and found that the non-demented patients exhibited impaired performance in phonemic fluency. This finding suggested that previous literature reporting semantic fluency deficits may have been a reflection of demented pathology rather than pure PD pathology. In addition to cohort demographics, the actual tasks themselves may be responsible for variation in results. Azuma *et al.* (1997) found that some letters are more difficult than others (e.g. "W" compared to "P"), in phonemic tasks, and that some categories are more difficult than other (e.g. "fruits" compared to "animals") in the semantic tasks. Thus, it can be seen how differential fluency results between studies could be a reflection of the relative disease state, educational level, and age of the PD cohorts, as well as the type of task administered. Never-the-less, most of the conducted studies have concluded that verbal fluency performance is not normal in PD, although whether the impairments are in phonemic or semantic tasks is yet to be resolved (for a meta-analytic review see Henry & Crawford, 2004). A matter of more importance, and indeed debate, is identifying the underlying cognitive processes that cause fluency impairments in PD.

1.6 Explanations of verbal fluency performance in PD

The considerable literature concerning PD performance in verbal fluency tasks has lead to the development of several theories to account for the observed results. Flowers, Robertson and Sheridan (1995) found that total word output in fluency tasks was around 20% lower in PD patients than in controls, with phonemic fluency being slightly more affected. The authors reported that the curve describing PD patients' word output rate over 5 minutes paralleled that of controls, but with relatively less words produced per minute. This demonstrated that PD performance essentially mirrored that of controls, except for the lower output rate. The authors attributed the results to the presence of bradyphrenia which suggests that PD word output was lower due to slowed information-processing abilities, rather than any specific difficulties with the task. However, it should

be noted that this study did not screen for dementia in PD patients which could have skewed the results, especially as the authors report that relative slowing was associated with disease severity. In fact, those patients in the early stages of the disease had word output rates equal to that of controls.

The study conducted by Matison *et al.* (1982) found that semantic fluency was impaired in PD patients whereas phonemic fluency remained intact. This prompted the authors to explain the deficit in terms of a word finding difficulty, specifically a semantic retrieval deficit. Auriacombe et al, (1993) also attributed impaired semantic fluency in PD patients to retrieval problems, but postulated that it was caused by a lexical retrieval deficit, rather than a word finding difficulties. This argument was supported in a later study by Randolph, Braun, Goldberg and Chase (1993) which investigated the affect of a cueing condition on semantic fluency. The authors reported that PD patients were impaired in the standard fluency task, but that the impairments disappeared when the cue condition was applied, thus suggesting that poor performance was due to deficit in retrieval strategy. The authors concluded that the retrieval deficit was related to a disruption in prefrontal functioning, suggesting that an underlying executive impairment was responsible for the fluency performance.

Some fluency studies such as Zec *et al.* (1999) have also investigated *alternating* fluency which requires participants to regularly switch between producing words within categories and producing words beginning with specified letters. Along with alternating fluency, the study also investigated semantic and phonemic fluency in PD, and found that PD patients were impaired relative to controls in the semantic and alternating fluency tasks. Zec *et al.* (1999) postulated that deficits arise in the alternating fluency task due to a failure of internal attentional control, an executive process, and suggested that poor performance in other fluency tasks is a reflection of the same impairment. Previous studies (Downes, Sharp, Costall, Sagar & Howe, 1993) investigating alternating fluency found that PD patients were only impaired in tasks which required switching between letters and categories (rather than just between different letters *or* different categories). The authors reported that PD word output was lower than controls under these conditions,

and that more perseverative errors were produced. According to the authors, results of this manner suggest that poor fluency performance is due to impaired inhibitory processes and a failure to maintain goal directed behaviour. Similar results were reported in an earlier study by Lees and Smith (1983) who also found that the biggest source of error in phonemic fluency tasks was perseveration. However, they suggested that the errors were a reflection of a set-shifting deficit in PD which prevented patients from efficiently switching between retrieval strategies, hence they were more likely to repeat the same words.

Overall, the literature on VF performance in non-demented PD is inconsistent, with some findings suggesting deficits in phonemic fluency but not semantic fluency, and vice-versa. In addition, there is considerable debate with regard to the cognitive nature of the observed fluency deficits. The discussed literature demonstrates the heterogeneity of PD profiles, and emphasises the importance of taking verbal ability, demographic factors and IQ into account when testing fluency performance. Furthermore, the disparity of results and the accompanying explanations suggests that using total word output as a performance marker in fluency tasks may not accurately reflect cognitive functioning.

1.7 Clustering and switching components in VF

The standard method of verbal fluency assessment, total word output, has been criticised by Troyer, Moscovitch and Winocur (1997) who claimed that although verbal fluency tests seemed to be sensitive to various neuropsychological disorders, very little could be inferred about the underlying cognitive process using word output alone. They postulated that there were two main processes required for successful fluency performance; clustering and switching. Clustering refers to the generation of words within semantic or phonemic subgroups, e.g. “cow, goat, sheep” (farm animals), or “press, present, predict” (*pr* words). Switching on the other hand refers to the number of shifts made between different cluster types. Troyer Moscovitch and Winocur (1997) investigated the clustering and switching performance of younger and older adults and found that both components were associated with the number of words generated in semantic tasks, whereas the switching component was more influential to word output in the phonemic

tasks. In addition, they reported that while cluster size remains stationary as age increases, switching rate decreases in older people, which suggested that switching was a more demanding task. To test this hypothesis, a divided attention paradigm was employed in which fluency tasks were administered in conjunction with a distracter task to increase the demand on the frontal lobes. The divided attention task caused fewer words to be generated, and fewer switches to be implemented in the phonemic task, but not the semantic task. This result indicated that the phonemic task was more sensitive to frontal functioning, and in addition, suggested that the switching component of fluency task is associated with frontal (executive) functioning. Clustering by contrast is assumed to be a more automatic process associated with the temporal lobes. Further evidence in support of this hypothesis was derived from clustering and switching performance in patients with temporal and frontal lesions (Troyer, Moscovitch, Winocur, Alexander & Stuss, 1998). Patients with fontal lobe lesions produced normal clusters sizes in phonemic and semantic fluency tasks, but failed to switch as often as controls, indicating that switching was indeed mediated by frontal areas. Temporal lesion patients were unimpaired on phonemic tasks but performed poorly in semantic tasks, however both clustering and switching components were affected. The results suggest that there is a dissociation between phonemic and semantic tasks, with phonemic being more associated with frontal functioning and semantic with temporal functioning. In addition, the results support Troyer Moscovitch and Winocur's (1997) hypothesis that switching is more associated with frontal functioning, especially in phonemic fluency tasks.

The clustering and switching methodology outlined above has subsequently been used to investigate fluency performance in PD. Troyer, Moscovitch, Winocur, Leach, and Freedman (1998) compared the two fluency components in demented and non-demented PD patients, as well as Alzheimer's patients. As expected, Alzheimer's patients were most impaired on the semantic task, whereas demented PD patients were more impaired on the phonemic task. Indeed, the performance pattern of clustering and switching was able to differentiate the two patient groups; Alzheimer patients produced smaller clusters in both tasks but only switched less in the semantic task, whereas demented PD patients switched less in both tasks but only produced smaller clusters in the phonemic task. This

pattern supports the notion that PD patients perform poorly on fluency tasks due to a executive deficit in the generation and control of retrieval strategies. However, somewhat surprisingly, the authors reported that the non-demented PD patients performed comparatively to controls in all the components of both fluency tasks.

A similar result was found in a study conducted by Troster *et al.* (1998), who investigated clustering and switching in several neurodegenerative diseases, including demented and non-demented PD, Alzheimer's disease and Huntingdon's disease. From all of the populations investigated, non-demented PD patients were the only group who performed normally on all measures of verbal fluency. This result prompted the authors to conclude that verbal fluency deficits in PD are a reflection of the dementia pathology rather than PD pathology itself. In contrast to this result, Donovan, Siegert, McDowall and Abernethy (1999) found that a cohort of non-demented PD patients were significantly impaired relative to controls in terms of total word output. Analysis of clustering and switching patterns revealed that PD patients made less switches than controls, but did not differ in their clustering performance. The authors explained the result in terms of compromised frontal functioning in PD groups manifesting in a specific switching impairment.

The studies described above, show a reasonable distinction between clustering and switching; clustering is consistently poorer in patients with damage to temporal areas, whereas switching is consistently impaired in patients with frontal damage and subcortical dementias in which frontal networks are implicated (including PD and Huntingdon's disease). The apparent inconsistencies between studies in the performance of non-demented PD switching may be a function of the small sample sizes employed (Troyer et al., 1998). However, the inconsistencies may also indicate that the method of clustering and switching devised by Troyer, Moscovitch and Winocur (1997) is not refined enough to be a reliable measure of the different fluency components.

The qualitative approach to analysis of clustering and switching in fluency tasks has been criticised for being an ambiguous reflection of performance (Mayr, 2002). The Troyer,

Moscovitch and Winocur (1997) methodology takes the amount of words per cluster and the number of switches made as a measure of lexical and executive processing respectively. This presents a problem because the number of switches made does not take into account the time spent retrieving words within clusters – if a participant spends a long time retrieving words within a cluster then consequently there will be less time for switching, and thus there will be fewer switches made (Mayr, 2002). Therefore, just reporting the number of switches made cannot determine whether PD patients have a problem retrieving words *within* clusters, switching *between* clusters, or a combination of both. Subsequently, Mayr (2002) suggested that clustering and switching analysis should be quantitative in nature, employing specific timing protocols to attain a precise measure of the *amount of time* spent retrieving words within clusters, and the *amount of time* spent switching between different clusters. Methodology of this type should give a far more accurate reflection of the nature of PD impairment in verbal fluency tasks.

1.8 Dissociating executive functioning and information-processing speed

Much of the evidence in the PD literature suggests that the exhibited cognitive impairments are a reflection of an underlying executive deficit (Owen, 2004; Zgaljardic *et al*, 2003). However, the possibility remains that the problems observed in cognitive tasks, including some executively demanding tasks such as verbal fluency, could be caused by slowed information-processing speed (Wilson et al, 1980; Flowers, Robertson & Sheridan, 1995). Analysis of the separate components of verbal fluency should help determine which domain of the task is causing impaired performance in PD. Clustering is thought to be a relatively automatic process, mediated predominantly by temporal areas, whereas switching has been shown to be more executively demanding and implicated processing in frontal areas (Troyer *et al.*, 1998). A deficit in information processing speed would presumably slow responses in both fluency components, whereas an executive deficit should affect switching performance specifically. However, fluency performance alone cannot dissociate executive dysfunction and slowed information processing speed. Even with the quantitative clustering and switching analysis, poor switching performance could be a reflection of slowed information-processing speed specific to executively demanding tasks (due to disruptions in frontostriatal circuitry, for example). Slow

clustering could be due to word retrieval problems or slowed information-processing speed within the lexical searches. It is therefore necessary to investigate word retrieval abilities and information-processing speed independently in PD populations. In addition, an attempt to dissociate executive dysfunction and information-processing speed can be made by investigating the affect of systematically increasing the executive load on the respective tasks.

1.9 Aims of the present study and hypotheses

The aim of the present study is to investigate the nature of the cognitive deficits observed in Parkinson's disease (PD), and specifically, to identify the underlying cause of the impaired verbal fluency performance exhibited by this group. The study aims to directly test two competing hypotheses regarding cognitive functioning in Parkinson's disease (information-processing speed vs executive dysfunction) in an effort to resolve which of these hypotheses is most pertinent to PD deficits. Clustering and switching analyses will be performed in verbal fluency measures following new methodology devised by Dr Abrahams which is consistent with the techniques outlined by Mayr (2002). In addition, the potential confounds of motor slowing in the PD population will be accounted for by employing a verbal fluency index (V*fi*) as devised by Abrahams *et al.* (2000). The affect of additional executive load on fluency performance will be examined by introducing a syllabic constraint to the fluency tasks in which participants will be required to generate words containing a specific number of syllables. Furthermore, a Numerical Information Processing (NIP A) task will be administered which has been adapted from the Adult Memory and Information Processing Battery (Coughlan & Hollows, 1985). The affect of additional executive load on information-processing performance will be investigated by the introduction of two further manipulations of the NIP task which require inhibition (NIP B), and working memory, attentional monitoring and decision making (NIP C). Background measures of intelligence, executive functioning, word retrieval, depression, and dementia sreens will also be employed to account for other potential pathologies.

Hypotheses

A strong inference approach was employed to develop the following differential hypotheses:

1). If slowed information-processing (bradyphrenia) is responsible for cognitive deficits in PD then it is postulated that, relative to controls;

- Patients will exhibit longer switching times *and* within cluster generation times in the standard spoken fluency task.
- Patients will exhibit longer verbal fluency indices in all the syllabic fluency conditions.
- Patients will exhibit longer written fluency indices in both the written fluency conditions
- Patients will be slower in all NIP task conditions, independent of their motor impairments.

2). If executive dysfunction is responsible for cognitive deficits in PD then it is postulated that, relative to controls;

- Patients will exhibit disproportionately longer switching times than within cluster generation times in the spoken fluency task.
- Patients will exhibit disproportionately longer verbal fluency indices as the syllabic constraints increase in the syllabic fluency task.
- Patients will exhibit disproportionately longer written fluency indices for the “C” word condition in the written verbal fluency task.
- Patients will exhibit normal performance in the basic NIP task, followed by disproportionate slowing in the conditions in which the executive demand increases.

2. Methods

2.1 Participants

Parkinson's disease patients

Eleven patients (8 men and 3 women) with Parkinson's disease were recruited from the Department of Clinical Neurosciences (DCN) clinic run by Dr. Richard Davenport at Western General Hospital, Edinburgh. Unfortunately, three patients had to be excluded from the final analyses. One patient was excluded on the basis of their Hospital Depression and Anxiety Scale score (HADS A = 10, HADS D = 12), which was considerably higher than any of the control participants. A further two were excluded because they were medicated by deep brain stimulation (DBS) which requires invasive brain surgery to establish electrical subcortical implants. The remaining cohort of eight patients (6 men and 2 women) had a mean age of 70.25 years (S.D. = 5.39; range = 62 – 77), and their mean years of education was 14.88 (S.D = 3.31; range = 9 – 20). Six of the patients were right-handed, and two were left-handed. The mean length of disease duration since diagnosis was 6.9 years (S.D. = 4.85; range = 2 - 15). Severity of Parkinson's disease in patients was assessed using the Hoehn and Yahr Parkinson's onset, progression, and mortality (POPM) scale (Hoehn & Yahr, 1967) which measures disease progression and motor ability. Five of the patients were rated at stage 1, two were rated at stage 3, and one patient was rated at stage 4 (see appendix F for stage classifications). None of the patients included in the analyses had a history of neurological problems, major medical or psychiatric illness, or learning disability. None of the patients had hearing or vision problems (vision corrected to normal with glasses). All patients were medicated for their PD symptoms, and all were in their "on" state during testing procedures. A breakdown of each patient's medications can be seen in Table 1. Seven of the patients were tested in their homes, and one patient came to the university.

Table 1. PD patient medication.

Patient No.	Type of Medication	Medication Details
1	Pramipexole	Dopamine agonist
2	Stalevo	Dopa decarboxylase inhibitor
3	Sinemet	Dopa decarboxylase inhibitor
4	Madopar	Dopa decarboxylase inhibitor
5	Sinemet, Sinemet+	Dopa decarboxylase inhibitor
6	Stalevo, Ropinirole	Dopa decarboxylase inhibitor, dopamine agonist
7	Sinemet+	Dopa decarboxylase inhibitor
8	Pramipexole	Dopamine agonist

Healthy controls

The patient group was compared to eight healthy control participants (4 men, 4 women), who were recruited via the department's volunteer participant panel. The controls and patients were matched in terms of age (mean = 70.25; S.D. = 5.70; range = 62 -77), and years of education (mean = 15.88; S.D. = 3.36; range = 12 – 20). Seven of the controls were right-handed, and one was left-handed. None of the controls had any history of neurological problems, major medical or psychiatric illness, or learning disability. None of the controls had vision problems (vision corrected to normal with glasses) however, two had mild hearing difficulties. Several controls were medicated with blood pressure regulators, but none were on any form of medication that could affect their cognitive performance. All controls were tested at the university, and received a modest reimbursement for their time spent testing.

2.2 Neuropsychological tests.

National Adult Reading Test (NART; Nelson & Willison, 1991)

The NART is a measure of pre-morbid intelligence that correlates very highly with standard intelligence measures such as the Wechsler Adult Intelligence Scale – Revised (WAIS-R). It is comprised of a list of 50 irregularly pronounced words of increasing difficulty. Participants are instructed to read the words aloud, and the number of errors is recorded and converted into an Intelligence Quotient (IQ) score.

Addenbrooke's Cognitive Examination Revised (ACE-R; Mioshi, Dawson, Mitchell, Arnold and Hodges, 2006)

The ACE-R consists of a variety of short subtests, and is used to assess cognitive functioning across five domains; attention/orientation, memory, verbal fluency, language, and visuospatial abilities. The ACE-R is commonly used as a cognitive screen with a score of 82 being the cut off for dementia (max. score = 100). The test also incorporates another cognitive screen, the Mini Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975).

Hospital Anxiety and Depression Scale (HADS; Zigmund & Snaith, 1983)

The HADS is a measure of emotional assessment used to screen for anxiety and depression. It is a self report questionnaire comprising of questions with multiple choice answers that are designed to be differentially sensitive to anxiety (HADS A score) and depression (HADS D score). However, the question "I feel as if I am slowed down" has exaggerated salience to PD patients who experience bradykinesia, and was therefore not included in the score. One participant (previously mentioned) had scores within the clinical levels for anxiety and depression and so had to be eliminated from the analyses.

Graded Naming Test (GNT; McKenna & Warrington, 1983)

The GNT is a test of confrontation naming that was included in the battery to assess word finding abilities in PD as this could potentially contribute to verbal fluency performance. The test comprises of 30 line drawings of uncommon words that increase in difficulty. Participants were asked to name the drawings, and the number of errors was recorded.

Hayling sentence completion test and Brixton spatial anticipation test (Burgess & Shallice, 1997)

The Hayling and Brixton tests are commonly used measures of executive functioning that have been shown to be sensitive to frontal dysfunction. The Hayling sentence completion test comprises of 2 sections which are always administered in the same order. In the first section, participants are read a series of 15 sentences in which the last word is missing.

The participant is required to respond as quickly as possible with a word that would appropriately complete each sentence. This section assesses response initiation, and participant responses are timed. The second section has the same structure as the first, however, the participant is required to complete each sentence with a word that has absolutely no relevance to the sentence itself. This section is more demanding and assesses response inhibition as well as strategy formation in producing an alternative intrinsically driven response. Responses in this section are also timed, and there is an additional error component to account for responses that are connected or somewhat connected to the probe sentence. Response times from the two sections and error scores from the second section are converted to an overall scaled score.

The Brixton spatial anticipation test comprises a booklet in which each page shows an array of ten circles, split into two rows of five. One circle in each page is coloured blue, and as the pages progress, the blue circle moves location in a logical pattern. The participant is shown a page and asked to predict where the blue circle will be on the subsequent page. Patterns are always evident in the test, however, the patterns change without warning, requiring participants to learn the new pattern quickly and adapt their predictions accordingly. This test assesses inhibition, set-shifting ability and working memory. Errors in predictions are tallied and converted into a scaled score.

2.3 Experimental tests

Spoken Verbal Fluency

The spoken fluency task employed by the study was adapted from Benton and de Hamsher's (1983) Controlled Word Association Test (COWAT) and assessed phonemic fluency. Participants must generate as many words as possible beginning with a specified letter in a 60 second time period. Three conditions were employed with the letters "P", "R", and "W" used respectively. Words beginning with the given letters occur in different frequencies in the English language; words beginning with "P" have the highest frequency, those beginning with "R" have a lower frequency, and those with "W" have the lowest frequency. Thus, the respective letter conditions require increasing cognitive

demand as the word frequencies decrease. In addition, a measure of total "PRW" output was calculated by adding the individual letter conditions together.

Syllabic Fluency

The affect of increasing executive demand on verbal fluency performance was investigated by developing a new syllabic manipulation of the spoken fluency task. As before, participants must generate as many words as possible beginning with a specified letter ("M" or "F") in 60 seconds. However, there were two discrete conditions employing syllabic constraints; in the first participants were instructed to generate words containing only 2 syllables, and in the second they were instructed to generate words containing 3 syllables only. Words beginning with the letters "M" and "F" have roughly the same frequencies in English, although the frequencies of 2 and 3 syllable words for each letter is not known. For this reason the letters were employed in a counterbalanced manner. Each syllabic constraint requires a more refined lexical search, as well as placing higher demands on the monitoring and inhibition of incorrect responses, thus imposing sequentially higher executive demands.

Written Verbal Fluency;

The written verbal fluency test (as described in Abrahams *et al.*, 1996) also assessed phonemic fluency. Two conditions were employed; in the first participants were asked to write down as many words as possible beginning with the letter "S" in 5 minutes. In the second condition, participants were asked to write down as many words as possible beginning with "C" in 4 minutes, however, the words produced had to contain only 4 letters. The "C4" condition is more executively demanding as it requires highly constrained search conditions and imposes greater demands on inhibition.

Procedure

In all fluency tasks, participants were instructed to avoid using plurals of a previously generated word (e.g. "peach, peaches"), and to avoid producing different endings of the same root word (e.g. "pot, potted, potter, potting"). As such, any examples of these were marked as errors. Perseverations (using the same word twice) were also considered

errors. The fluency tasks were scored in terms of the number of correct words generated for each condition. Spoken verbal fluency tasks were filmed using a Canon HDV video-camera so that clustering and switching analyses could be performed at a later date.

Fluency Index

Fluency tasks are essentially time based and involve a motor response (either spoken or written), and as such they will be affected by slowed motor functioning evident in PD. To control for this issue, the current study employed a Verbal Fluency Index (VFi), as devised by Abrahams *et al.* (2000). Each fluency task employed a generation condition (as described above), and a motor control condition in which participants read aloud or copied the words they generated previously. This procedure provided a measure of the same motor responses required in the generation conditions, but without the cognitive requirements of each task. Thus, indices of the *average* time to think of a word could be calculated that were independent of motor functioning; VFi's were calculated as follows;

$$\text{Verbal Fluency Index (VFi)} = \frac{\text{Total Generation Time} - \text{Control Copy/Read Time}}{\text{Number of Items Generated}}$$

Errors (perseverations and any words which broke the fluency rules) were excluded from the VFi calculations. Separate VFi's were calculated for each fluency condition as well as an average for all the letters conmbined.

Clustering and Switching Analysis

The number of words generated during a spoken fluency task does not give an indication of the *nature* of any underlying problem. Therefore, the time taken to generate words within clusters, as well as the time taken to switch between clusters was calculated for the standard spoken fluency conditions (P, R, and W). Generation of words *within* clusters is assumed to be a relatively automatic task as related words share activation patters within the lexical system. Clustering refers to the production of two or more words that are related, either phonemically or semantically (e.g. p*a*t, p*a*st, p*a*nt, or pencil, paper, pen). Other cluster types included in the analyses are overlapping clusters in which a word

from one cluster forms a link to another cluster, and single clusters for which no immediately surrounding words that can be linked phonemically or semantically. These types of cluster were not included in the cluster analysis, but were accounted for in the switching analysis. Errors and perseverations were included in the analysis as they could be integral to the cluster formation. For the full clustering criteria see the appendices. The clustering measure was also designed to control for impaired motor production by including the time taken to read each cluster in the analyses. The average time taken to generate a single word within a given cluster was calculated by subtracting the time taken to read the words within the cluster from the time taken to generate the cluster and dividing by the number of clusters minus one:

$$\text{Single Cluster Time} = \frac{\text{Time to generate cluster} - \text{Cluster Read Time}}{\text{Number of Words in Cluster} - 1}$$

The average cluster time for a particular condition was calculated by adding the individual cluster times for that condition together, and dividing by the number of clusters as follows:

$$\text{Cluster Time} = \frac{\text{Sum of single cluster times}}{\text{Total number of clusters}}$$

Switching refers to the generation of, or shift to, a different strategy to retrieve words (e.g. from p*a*nt to *pr*ess, or from paper to pull). Switching requires effortful executive functioning to generate and shift between retrieval strategies and is associated with frontal functioning. Switching time for each condition was calculated by subtracting the total time required to generate all clusters (including single and overlapping clusters) from the total task time (i.e. 60 seconds) and dividing by the total number of clusters:

$$\text{Switch Time} = \frac{\text{Task Time} - \text{Total Cluster Generation Time}}{\text{Total Number of Clusters}}$$

In addition, the mean switching and clustering time across all letters was derived by adding the times of the respective letters together, and dividing by the number of conditions:

$$\text{AVG Cluster/Switch Time} = \frac{\text{Sum of P, R, W Cluster/Switch Times}}{\text{Number of Conditions (3)}}$$

Numerical Information Processing (NIP) task;

The NIP task was developed to directly investigate the affect of executive load information-processing speed. The numerical information-processing (NIP) task design was based on the information-processing subtest of the Adult Memory Information-Processing Battery (AMIPB; Coughlan & Hollows, 1985). The basic (NIP A) task comprised of 30 rows of 5 double-digit numbers; participants were required to identify the highest digit from each row by crossing it out. This task involves a sensory search and motor component, but it is executively undemanding, and is therefore a good measure of information processing speed. However, in order to differentially test executive functioning in the same task, two further conditions were employed. The first condition simply involved the identification of the second-highest number, and therefore required inhibition of the highest number response (NIP B). The second condition was more executively demanding as it requires an arithmetical estimation component – participants were required to identify whether or not the middle number in each row is greater or smaller than the lowest number doubled (NIP C). This arithmetic condition is executively demanding as it requires working memory, strategy formation, and attentional monitoring. Thus, the NIP task investigates information-processing performance with an increasing executive demand that should facilitate a dissociation between the two processes.

In all conditions, the speed and accuracy of the responses were taken as a measure of NIP performance. As in the fluency tasks, impaired motor production can be accounted for by the inclusion of a motor control condition. Participants are required to cross through numbers that were already identified as the correct responses, thus eliminating any

cognitive demand of the task but retaining the same motor component. The time taken to complete the control condition is deducted from the experimental conditions to give an index of information-processing speed independent of motor dysfunction:

NIPi = NIP Time – NIP Motor Control Time.

Full details of all the verbal fluency measures including participant instructions and scoring criteria can be found in appendices A and B. Details of the NIP tasks are in appendix C.

2.4 Procedure

The full test battery took between 2 and 2.5 hours to complete, and participants typically took a break about halfway through to avoid fatigue. Participants' responses during the spoken verbal fluency tasks were digitally recorded using a Canon HDV video camera, so that clustering and switching analyses could be performed at a later date. A stop watch was used to monitor the time taken to complete tasks and in conditions which require reaction time scoring. Clustering and switching timed analyses were performed on a laptop using Power DVD software. The study was approved by ethics boards of the NHS Lothian and the University of Edinburgh School of Philosophy, Psychology and Language Sciences (PPLS). Written informed consent was obtained from all patients and control participants.

2.5 Statistical design

Given the small sample size, all variables within the data set were explored for normal distribution using histograms and the Shapiro-Wilk test of normality. In addition, all variables were checked for homogeneity of variance. One outlier was removed from the control group in the "W" condition and total "PRW" condition because the participant did not complete the task properly. Scores for this participant were more than 2.5 standard deviations from the mean and forced the distribution into abnormality. The only other missing values were the Written Verbal Fluency values of one PD patient who was

unable to write due to his motor difficulties, and one patient's GNT assessment that was not conducted due to time constraints.

Comparative group analyses of patient and control means were performed using t-tests in normally distributed populations. In populations that were not normally distributed comparative group analyses were performed using the Mann-Whitney U test. The one-tailed probability level was adopted for tests with a predicted directional result. Repeated measures analyses were performed using a two-way mixed analysis of variance (ANOVA) to investigate the effect increasing executive load in both groups. The between-group factor was group (PD patients vs controls), and the within-subjects factor was executive load (various measures). In addition to standard analyses, any abnormally distributed data that consisted of reaction times were log transformed to account for potential skewed distributions.

3. Results

3.1 Participant characteristics

Patients and controls were matched in terms of age (t (14) = 0; p = 1.00, non-significant), and years of education (t (14) = -0.6; p = 0.56, n.s). In addition, the NART scores of patients and controls did not differ significantly (t (14) = -1.35; p = 0.2) suggesting that the groups were well matched in terms of pre-morbid IQ. Group means and standard deviations for these measures can be seen in Table 2.

3.2 Neuropsychological assessment: Comparative analyses

Table 2 shows the groups means for participant demographics and neuropsychological assessment. There was a significant different between groups in ACE-R performance (t (14) = -2.8; p < 0.01) suggesting that patients' cognitive functioning had been affected by PD. However, none of the patients had an ACE-R score of less than 82 (specificity for dementia), indicating that there were no demented patients in the cohort. Group differences in the HADS A and HADS D scores were not significant; (U = 29.0; exact p = 0.395, one-tailed) and (U = 19.5; exact p = 0.107, one-tailed) respectively, and all individual scores were below the clinical criteria. As can be seen in Table 2, PD group's average GNT score was lower than the control group suggesting that there may have been some mild word finding difficulties in the PD cohort. However, this difference just failed to reach significance (t (13) = 1.5; p = 0.08, one-tailed).

Assessment of executive functioning revealed significant group differences in the Hayling sentence completion test (U = 4.5; exact p = 0.001, one-tailed) and Brixton spatial anticipation test (U = 10.0; exact p = 0.011, one-tailed). This result suggests that the observed group differences on these tasks are a reflection of poorer executive functioning in the PD group. However, it should be noted that only one PD patient met the criteria for *impaired* task performance on the Hayling test, and no participants met this criteria in the Brixton test.

Table 2. Participant demographics and neuropsychological assessment; group means and standard deviations shown in parentheses.

Variable	PD Patients	Controls
Age	70.25 (5.39)	70.25 (5.70)
Education	14.89 (3.31)	15.89 (3.36)
NART Full Scale IQ	117.89 (7.26)	122.38 (6.02)
ACE-R (max = 100)**	92.0 (4.04)	96.75 (2.60)
HADS A	3.5 (2.33)	3.63 (2.20)
HADS D	2.13 (1.55)	1.13 (1.0)
GNT Errors	5.71 (3.99)	3.25 (2.25)
Hayling**	3.75 (1.83)	6.63 (0.92)
Brixton*	4.63 (1.41)	6.25 (0.87)

* Indicate variables for which there were significant group differences ($p < 0.05$), ** ($p < 0.01$)

3.3 Experimental tests

Spoken verbal fluency (P, R, W) – word output

Table 3 shows that PD patients generated fewer words than controls in all letter conditions. Group analyses were performed on the word output scores which revealed significant differences in all the spoken fluency letter conditions; "P" ($t(14) = -2.87$; $p < 0.01$), "R" ($t(14) = -2.11$; $p < 0.05$), and "W" ($t(13) = -4.15$; $p < 0.01$). This result was expected, and confirms the assumption that PD patients perform poorly compared to controls on standard measures of fluency. In addition, the word output for all letters combined (PRW condition) was analysed. Significant group differences in total word output were confirmed ($t(13) = -3.0$; $p < 0.01$). However, these analyses do not take impoverished motor functioning into account and therefore may be unreliable.

Table 3. Spoken verbal fluency group means and standard deviations in ().

Fluency Condition	PD Patients	Controls
P Word Output**	13.5 (4.24)	19.25 (3.77)
R Word Output*	12.5 (4.69)	17.25 (4.30)
W Word Output**	10.88 (3.48)	18.0 (3.11)
PRW Word Output**	36.88 (11.80)	53.71 (9.60)
VFi.P**	3.88 (1.36)	2.41 (0.68)
VFi.R*	4.69 (2.33)	2.98 (1.31)
VFi.W**	5.39 (2.24)	2.69 (0.59)
AVG.VFi*	4.65 (1.89)	2.76 (0.74)

* Indicate variables for which there were significant group differences ($p < 0.05$), ** ($p < 0.01$)

Spoken verbal fluency – fluency index (VFi)

The verbal fluency indices detailed earlier could account for motor problems in the PD population. Comparative analyses were performed on the fluency indices of patients and controls across all letters (PRW) to produce an Avg.VFi. This measure revealed a significant difference between groups ($t(13) = 2.48$; $p = 0.014$) showing that on average, PD patients spent longer generating each word than controls. Table 3 shows that the fluency indices of the PD group were longer than that of controls indicating that they spent more time generating each word in the P, R, and W conditions. Group analyses of verbal fluency indices revealed significant differences between patients and controls in all the letter conditions; VFi.P ($t(14) = 2.73$; $p < 0.01$), VFi.R ($U = 14.0$; exact $p = 0.032$), and VFi.W ($t(13) = 3.27$; $p < 0.01$). This result suggests that even when motor impairments are controlled for, PD patients still perform poorly in fluency tasks relative to controls. The relationship between group VFi performance and letter condition is represented in Figure 3.

Fig. 3. Graph of group VFi means for the spoken verbal fluency letter conditions

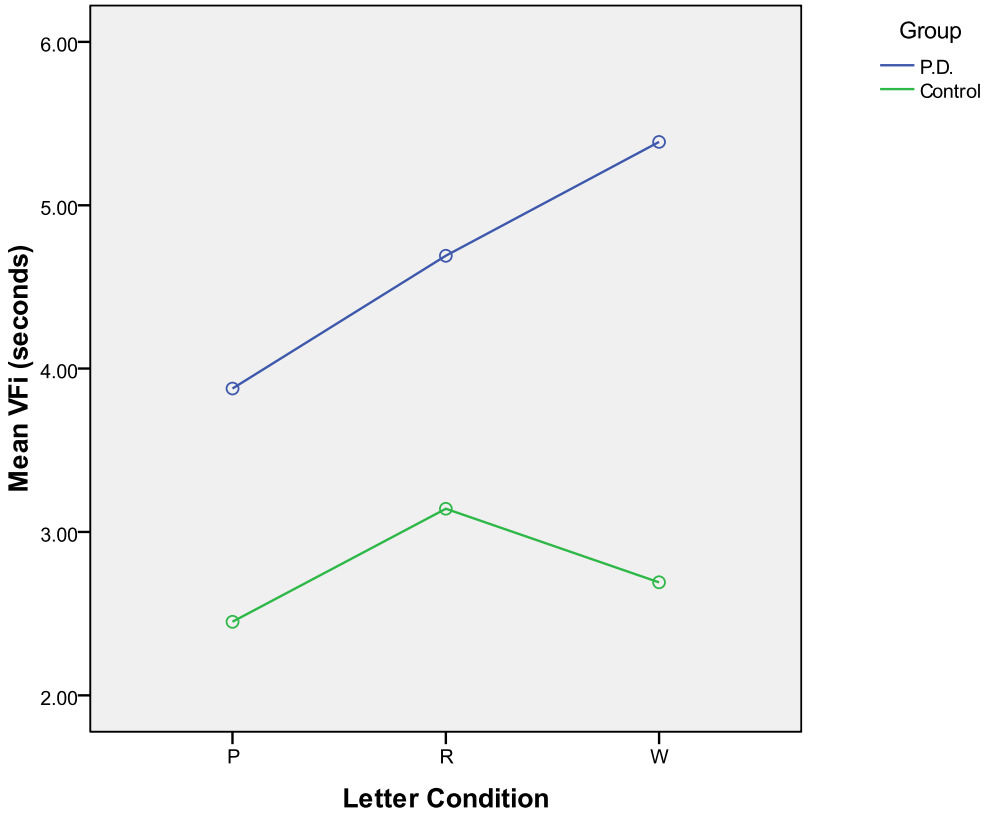


Figure 3 clearly shows the group differences in all letter conditions. It also suggested that each letter in the spoken fluency task was progressively harder for PD patients but not for controls. In addition there appeared to be a trend towards an interaction in which the PD group had a VFi in the W condition that was disproportionately longer than that of controls.

Spoken verbal fluency – errors and perseverations

Comparative group analyses revealed no differences between PD patients and controls for errors or perseverations in any of the letter conditions; P errors (U = 25.0; exact p = 0.29), P perseverations (U = 23.5; exact p = 0.22), R errors (U = 27.0; exact p = 0.32) R perseverations (U = 25; exact p = 0.29), and W errors (U = 24.0; exact p = 0.37), W perseverations (U = 23.5; exact p = 0.37). This result indicated that differences between

PD and control performance in fluency tasks is unlikely to be a reflection of perseverative errors in PD patients. Raw data for this measurement is reported in appendix D.

Spoken verbal fluency – clustering and switching

The experimental tests included manipulations designed to increase the executive demands of the task and thus investigate whether PD patients are disproportionately worse than controls on tasks requiring high executive load. In the spoken fluency tasks, clustering time (low executive load) was compared to switching time (high executive load), using a two-way mixed ANOVA. The between-subjects factor was Group (PD patients vs controls) and the within-subjects factor was Fluency component (clustering vs switching). The group means for clustering and switching times in each letter condition as well as the averages across letters can be seen in Table 4. The data met the normality criteria (Shapiro-Wilk test).

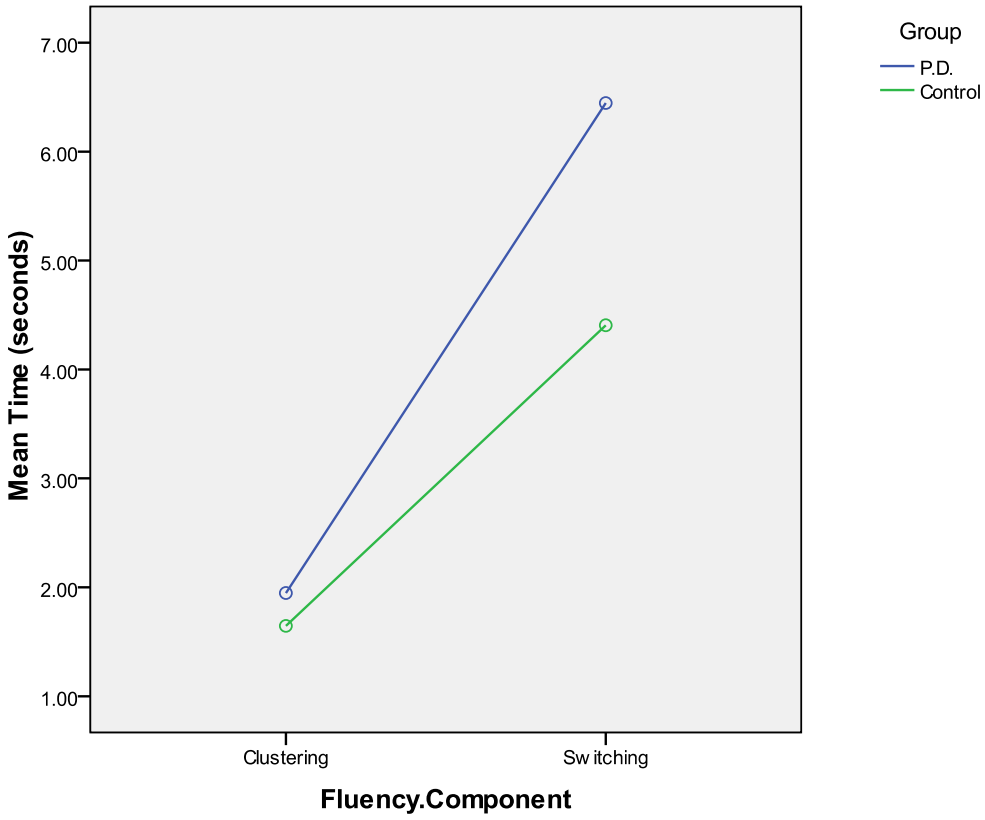
Table 4. Group means for clustering and switching times with standard deviations in parentheses

Fluency Condition	PD Patients	Controls
P Cluster Time	2.16 (1.48)	1.38 (0.92)
R Cluster Time	1.61 (0.82)	1.81 (0.71)
W Cluster Time	2.07 (1.22)	1.84 (0.82)
P Switch Time	4.77 (1.44)	4.00 (1.23)
R Switch Time	6.66 (2.78)	4.97 (2.82)
W Switch Time	7.92 (2.42)	4.06 (1.28)
AVG Cluster Time	1.95 (0.99)	1.65 (0.77)
AVG Switch Time	6.45 (1.80)	4.41 (1.43)

The mixed ANOVA for the average clustering and switching times across all letter conditions revealed a significant main effect of Fluency component ($F(1, 13) = 47.87$; $p < 0.01$. Partial eta squared 0.79 representing a large effect size). This result indicated that switching times were longer than clustering times in all participants and for all letter conditions. In addition, there was a significant effect of Group ($F(1, 13) = 7.05$; $p < 0.05$. Partial eta squared 0.31 representing a large effect) but no significant interaction (F (1,

13) = 2.74; p = 0.12). This result indicated that on average, PD patients were slower in both clustering and switching measures; a finding that is consistent with the slowed information-processing hypothesis of PD performance. However, the relationship observed in Figure 4 seemed to suggest that PD patients were disproportionately slower on the switching component which supports the executive dysfunction hypothesis. A significant interaction may not have been found due to low study power.

Fig. 4. Graph showing the group means for clustering and switching times.



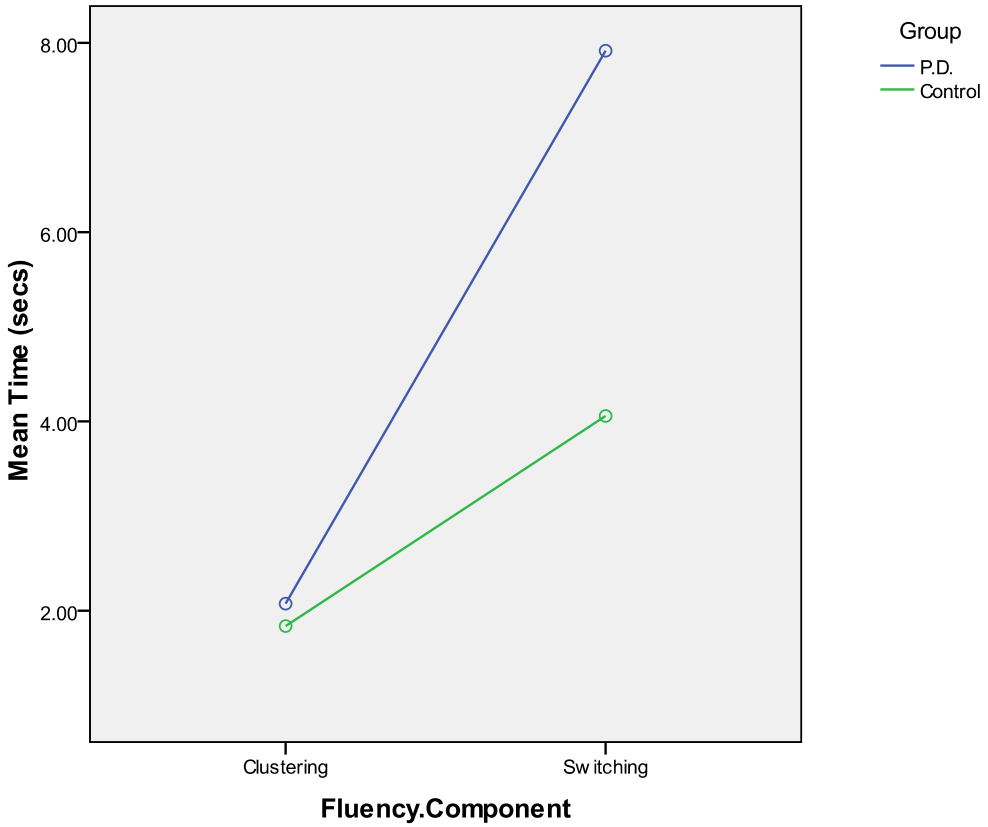
To investigate the group patterns of clustering and switching performance in more detail, mixed ANOVA's were employed in each letter condition. The mixed ANOVA for clustering and switching comparisons in the P condition revealed a significant main effect of Fluency component (F (1, 14) = 47.19; p < 0.01. Partial eta squared = 0.77 representing a large effect) showing that all participants were spending more time

switching than clustering. The effect of Group however was not significant ($F(1, 14) = 2.21$; $p = 0.159$) and there was no interaction between fluency component and group ($F(1, 14) = 0$; $p = 0.989$) suggesting that PD patients performed comparatively to controls in this condition.

A similar pattern of results emerged in the R condition. The mixed ANOVA revealed a significant main effect of Fluency component ($F(1, 14) = 28.12$; $p < 0.01$. Partial eta squared = 0.67 representing a large effect) suggesting that all participants had longer switching times than clustering times. Once again there was no significant effect of Group ($F(1, 14) = 1.22$; $p = 0.287$) and no interaction ($F(1, 14) = 1.49$; $p = 0.243$) suggesting that PD patients and controls performed comparatively on this measure as well.

The W condition produced a different pattern of results. The mixed ANOVA revealed a significant main effect of Fluency component ($F(1, 13) = 35.01$; $p < 0.01$. Partial eta squared = 0.729 representing a large effect) which suggested once again that all participants had longer switching times than clustering times. In addition, a significant effect of Group was found ($F(1, 13) = 19.9$; $p < 0.01$. Partial eta squared = 0.61 representing a large effect size), and crucially a significant interaction between fluency component and group was also apparent ($F(1, 13) = 7.08$; $p < 0.05$. Partial eta squared = 0.35 representing a large effect). This result indicates that PD patients had disproportionately slower switching times than controls in this letter condition. The interaction can be seen in Figure 5.

Fig. 5. Graph showing the group means for switching and clustering times in the W condition



The clustering and switching analyses have supported the assumption that switching is a more demanding task than clustering, as group means were consistently significantly longer for the switching measure. Furthermore, the letter condition “W” showed a significant interaction between group and fluency component indicating that PD patients spent disproportionately more time than controls switching in the most demanding fluency condition. This may reflect an executive dysfunction in PD patients that manifests itself only when the task is already demanding.

Syllabic fluency

The syllabic fluency condition was designed to increase the executive demands of the standard spoken fluency task. Participants were given a letter of the alphabet ("M" or "F") and required to generate words containing two syllables in the first condition, and words containing three syllables in the second condition. Table 5 shows the group means from the 2 syllabic conditions; log transformed data were used in the subsequent verbal fluency index (VFi) analyses because these data distributions were abnormal.

Table 5. Syllabic fluency group means and standard deviations in () and log transformed data in italics.

Fluency Condition	**PD Patients**	**Controls**
2 Syllable Word Output	4.75 (3.88)	10.0 (1.93)
3 Syllable Word Output	4.13 (3.31)	6.25 (2.12)
VFi.2	27.32 (26.59) *2.81 (1.09)*	5.32 (1.47) *1.64 (0.27)*
VFi.3	21.03 (17.65) *2.77 (0.80)*	9.64 (4.49) *2.19 (0.41)*

N.B. Standard deviation of PD patient's VFi.2 is very large due to some patient's failure to produce a single word, resulting in very large fluency indices.

Repeated measures analyses were performed on the transformed VFi syllabic fluency data using a two-way mixed ANOVA where Group was the between-subjects factor (patients versus controls) and Executive load was the within-subjects factor (VFi 2 syllables versus VFi 3 syllables). The analyses showed no significant main effect of Executive load ($F(1, 14) = 1.28$; $p = 0.28$). However, there was a significant effect of Group ($F(1, 14) = 9.64$; $p < 0.01$. Partial eta squared = 0.41 representing a large effect) suggesting that PD patients spent longer generating each word in both the syllabic tasks; a finding in support of the slowed information-processing speed hypothesis. There was no significant interaction between Group and Executive load ($F(1, 14) = 1.72$; $p = 0.21$). The lack of an Executive load effect may be explained by PD patients' floor performance in this task; this is illustrated in Figure 6.

Fig. 6. Graph of group VFi means (log transformed) for the syllabic fluency conditions

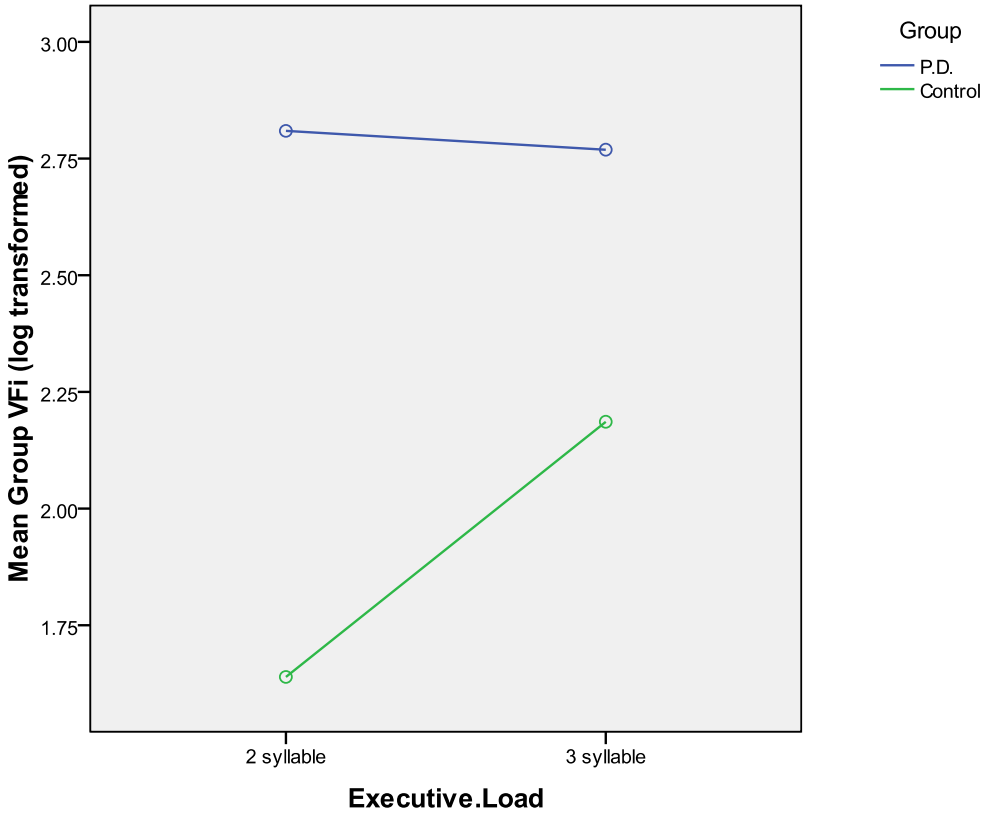


Figure 6 indicates that there may well be an effect of executive load in the syllabic fluency conditions as control participants showed longer VFi's in the 3 syllable condition than in the 2 syllable condition. However, this potential effect may have been masked by floor performance of the PD patients in both conditions as suggested by the significant effect of Group.

Given the observed difference in group performance, is it was of interest to compare PD patients performance in this task to their performance in standard fluency conditions. Unfortunately, this analysis could not be performed directly as the standard spoken fluency task and the syllabic fluency tasks were administered independently and employed different letters. However, Figure 7 shows the potential interaction between the VFi measures (log transformed) for the standard P condition and the 2 syllable condition.

Fig. 7 Graph of group VFi means (log transformed) for P condition and 2 and 3 syllable conditions

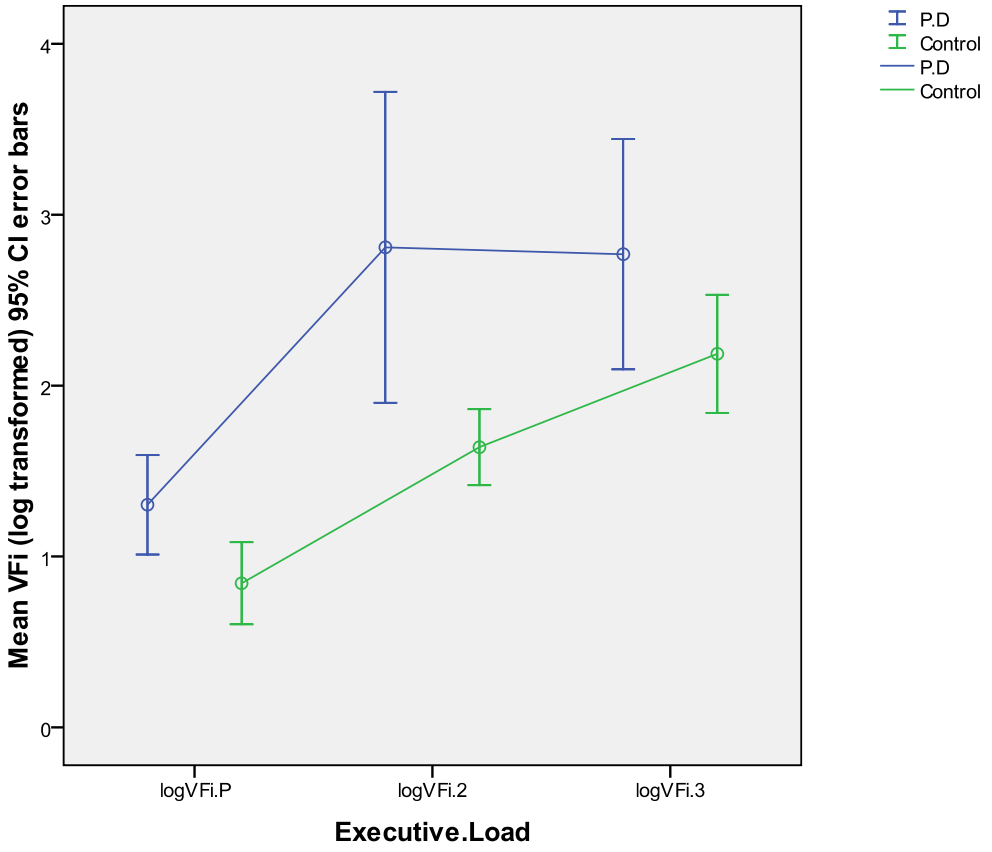


Figure 7 indicates that generating words beginning with F or M in the 2 syllable condition took longer than generating words in the P condition (no syllabic constraint). This relationship suggests that the syllabic constraint imposed greater executive demands by requiring more stringent search and monitoring criteria. Mean group differences are apparent across all the conditions, and crucially, there is no overlap between the PD and control error bars in the 2 syllable condition. This is indicative of a significant interaction, suggesting that the PD group had a disproportionately longer VFi than the control group in the 2 syllable condition. In the 3 syllable condition the control VFi was longer again, however the PD group showed a plateau effect suggesting that they were performing at floor level.

Written verbal fluency – word output

Table 6 details the written fluency means, and shows that the PD group produced fewer words and had higher fluency indices (i.e. longer times to think of each word) in both letter conditions. However, analysis of the written verbal fluency group means for the total words generated across both letters (SC condition) was not significant (t (13) = -1.53; p = 0.075) although this relationship was trending towards significance. Individual letter analyses of the group means for word output revealed significant differences between patients and controls for the "S" condition (t (13) = -1.87; p = 0.042), but not for the "C with 4 letters" (C4) condition (t (13) = -0.83; p = 0.22). This result is somewhat surprising as the C4 letter condition was designed to be more demanding and therefore PD patients were expected perform disproportionately worse in this condition than in the S condition.

Table 6. Written verbal fluency group means and standard deviations in ().

Fluency Condition	PD Patients	Controls
"S" Word Output*	34.29 (14.94)	46.75 (10.79)
"C4" Word Output	15.14 (11.77)	19.13 (6.47)
SC Word Output	49.43 (26.25)	65.88 (14.37)
wVFi.S*	6.76 (3.20)	3.81 (2.02)
wVFi.C4	22.41 (15.42)	11.51 (5.18)
AVG.wVFi*	14.58 (9.15)	7.66 (3.27)

* Indicate variables for which there were significant group differences ($p < 0.05$), ** ($p < 0.01$)

Written verbal fluency – fluency index (wVFi)

A similar pattern of performance was reflected in the group analyses of the written fluency indices for the "S" and "C4" conditions; (t (13) = 2.16; p = 0.025), and (t (13) = 1.78; p = 0.059) respectively. However, it should be noted that the wVFi for the "C4" condition very nearly reached significance suggesting that there may have been a real effect between patients and controls in this condition after all. Moreover, analysis of the average written fluency index (Avg.wVFi) for both letters did show a significant group difference (t (13) = 2.01; p = 0.033) indicating that on average, PD patients did spend

more time generating each word than controls. The results from the written fluency task are not completely consistent, but the overall trend does suggest the PD patients performed worse than controls on this measure. However, unexpectedly PD patients did not show worse performance on the C4 condition than the S condition. The pattern of group performance in the written fluency indices is shown in Figure 8.

Fig. 8. Graph of wVFi group means in the S and C4 written fluency conditions

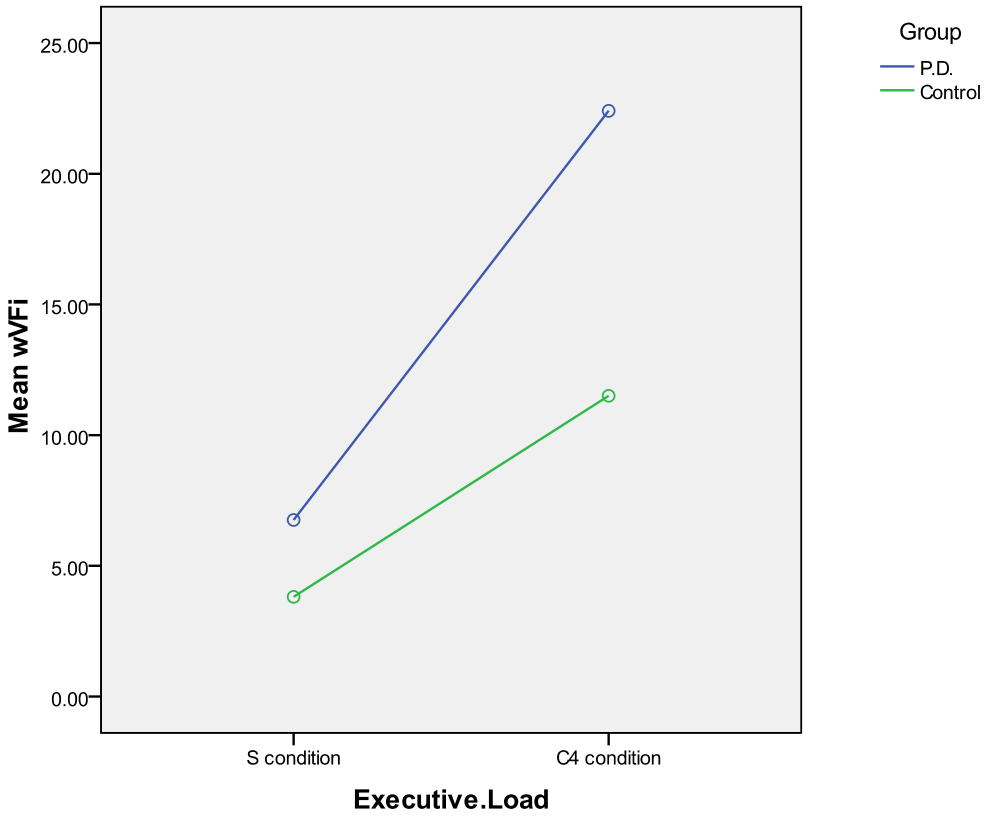


Figure 8 clearly shows the average group differences evident in the comparative wVFi analyses. It also indicated that the C4 condition was more demanding than the S condition for both groups. In addition there appeared to be a trend towards an interaction in which the PD group had a mean wVFi in the C4 condition that was disproportionately longer than that of controls. It is difficult to judge the results of the written fluency task in terms of the hypotheses. The average group difference in wVFi and lack of significant

interaction support the slowed information-processing account, however, the graph suggests a possible interaction which is consistent with an executive dysfunction.

As in the other verbal fluency tasks, there were no significant differences between the groups in the errors or perseverations made in both written fluency conditions; "S" errors (U= 22.0; exact p = 0.231), "S" perseverations (U = 18.5; exact p = 0.128), and "C" errors (U = 20.0; exact p = 0.192), "C" perseverations (U = 19.0; exact p = 0.179). Raw data for this measurement is reported in appendix D.

Numerical Information Processing (NIP)

The NIP tasks were designed to investigate the affect of increasing executive demand on participants' information-processing speed. Table 7 shows the group means for the NIP task.

Table 7. Numerical Information Processing index group means (seconds) and standard deviations in ()

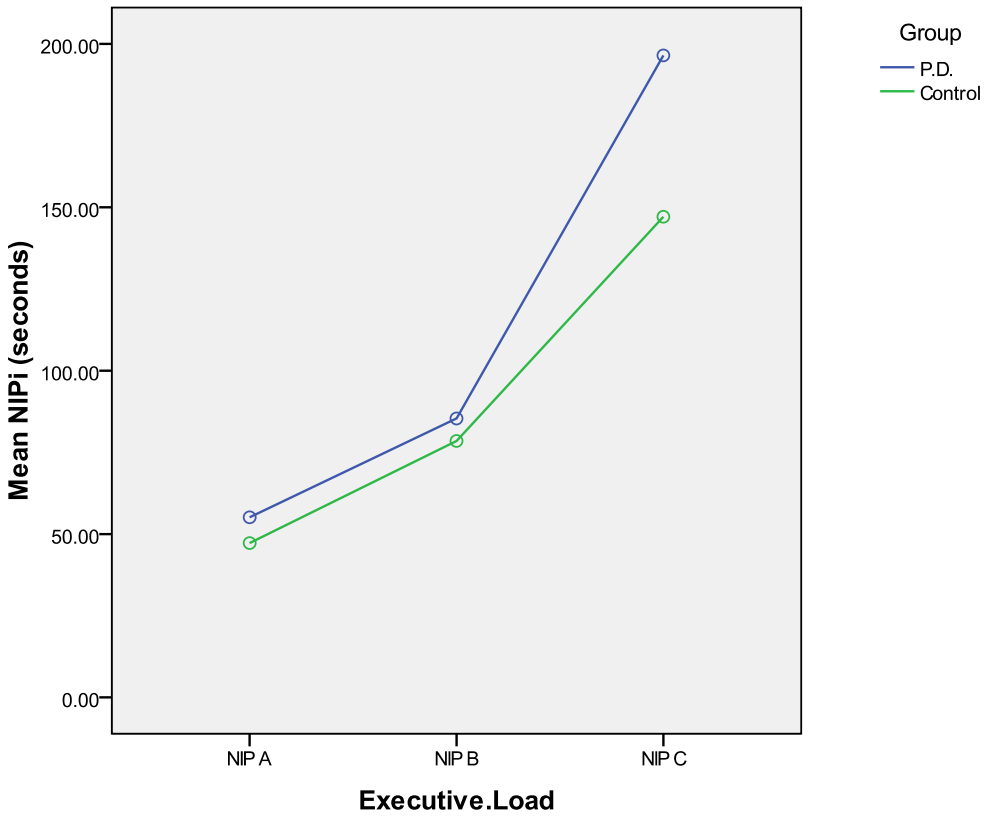
NIP Condition	PD Patients	Controls
NIPi.A	55.13 (10.45)	47.25 (12.01)
NIPi.B	85.38 (18.75)	78.5 (16.58)
NIPi.C*	196.5 (52.79)	147.13 (27.06)

* Indicate variables for which there were significant group differences ($p < 0.05$), ** ($p < 0.01$)

A two-way mixed ANOVA was performed to investigate the effect of executive load on information-processing speed performance. The between-subjects factor was Group (PD patients versus controls) and the within-subjects factor was Executive load; 3 levels; NIP A (no load), NIP B (low), and NIP C (high). The data met the normal distribution criteria. The ANOVA revealed a significant main effect of Executive load ($F (2, 28) = 121.77$; $p < 0.01$. Partial eta squared = 0.9 representing a large effect) and a significant effect of group ($F (1, 14) = 4.70$; $p < 0.05$. Partial eta squared = 0.25 representing a large effect). In addition, there was a significant interaction between Group and Executive load (F (2,

28) = 4.56; $p < 0.05$. Partial eta squared = 0.25 representing a large effect). The result is well represented in Figure 9.

Fig. 9. Graph of group NIP indices for NIP A, NIP B and NIP C conditions



The significant effects of the two-way mixed ANOVA and Figure 9 show that the NIP conditions required increasingly longer completion times suggesting that they imposed sequentially greater executive demands. Group differences are apparent in all conditions suggesting that PD patients were slower than controls in all the conditions. However, the significant interaction, and the form of the graph suggested that PD patients were disproportionately slower than controls in the NIP C condition (high executive load). Further investigation into the nature of the effects was performed using comparative analyses (t-tests) as pair-wise comparisons in SPSS were not possible.

The comparative analyses revealed that group differences in the NIP A and NIP B conditions were not significant; ($t(14) = 1.40$; $p = 0.092$) and ($t(14) = 0.78$; $p = 0.225$) which suggested that the PD group performed comparatively to the control group in information-processing speed tasks with low or no executive demand. By contrast, the group differences in the NIP C condition were significant ($t(14) = 2.35$; $p = 0.017$) suggesting that the PD group were only slower in the information-processing task when it imposed a high executive demand. The results from the NIP task clearly support the hypothesis that a specific executive dysfunction is responsible for poor PD performance in this task.

Comparative analyses were also employed to investigate the number of errors made in each condition and showed that there were no significant differences between the groups; NIP A errors ($U = 21.0$; exact $p = 0.151$), NIP B errors ($U = 24.5$; exact $p = 0.23$), and NIP C errors ($U = 22.0$; exact $p = 0.16$). Raw data for this measurement is reported in appendix E.

4. Discussion

4.1 Study findings and implications

The current study investigated the patterns of impairment exhibited by PD patients in verbal fluency tasks. The main aim of this investigation was to determine whether the observed impairments in PD reflect an underlying information-processing speed deficit (bradyphrenia), or a more specific executive dysfunction. The study employed a method of clustering and switching analysis that measured the *time* spent on each component of fluency tasks in an effort to dissociate automatic and effortful processing. In addition, the study employed two novel experimental paradigms which were designed to systematically increase the executive load on a standard fluency task and an information-processing task. All experimental measures in the current study were designed to control for the impoverished motor abilities that characterise PD.

Standard measures of neuropsychological assessment were also employed by the study to screen for potential confounding disorders in the patient population, and to aid in the selection of accurately matched control participants. The patient and control groups were well matched in terms of age and years of education, and this was reflected by NART Full Scale IQ scores that were non-significant. This was an important finding as any subsequent significant differences found in other measures were more likely to reflect changes associated with PD rather than pre-morbid differences in intellectual ability. The ACE-R assessment resulted in significant differences between the groups suggesting that PD does have a detrimental effect to cognitive functioning, especially given the fact that the other intellectual measures were matched. The HADS assessment showed that there were no significant differences between patients and controls in the anxiety or depression scales indicating that group differences were not a reflection of elevated depressive symptoms in the PD group.

Some researchers have postulated that verbal fluency deficits in PD may be a result of low level word retrieval difficulties (e.g. Matison *et al.*, 1982). Although group differences in the GNT were non significant, there was a trend towards significance suggesting that mild word finding difficulties may contribute to verbal fluency

impairments in PD. Further investigations should continue to explore word retrieval abilities in PD in an effort to resolve this issue. Several researchers have attributed PD impairments in cognitive functioning to an executive dysfunction (e.g. Zgaljardic, 2003; Owen, 2004), and indeed this is one of the hypotheses considered in the current study. The Hayling sentence completion and Brixton spatial anticipation tests produced significant group differences reflecting the low scores of the PD cohort in these measures. Although only one PD patient was *clinically* impaired on these tests, the results are indicative of relatively poor PD performance in the executive domain. Given that the patients performed comparatively to controls in the GNT, the results from the Hayling and Brixton support the hypothesis that an executive dysfunction may underpin fluency impairments in PD.

The investigation of verbal fluency performance employed a number of different methodologies. In terms of the total word output, PD patients produced significantly fewer words than controls in the standard measure of spoken verbal fluency (PRW total), as well as in each of the individual letter conditions. Thus, the results of the current investigation support the findings of previous phonemic fluency studies in suggesting that PD patients are impaired in this measure (Bayles *et al.*, 1993; Azuma *et al.*, 1997). The results of the written verbal fluency task were less clear cut; PD patients did not differ significantly from controls in terms of the total words generated across both letters (S and C), however the relationship did trend towards significance. Analyses of the individual letters showed that patients produced significantly fewer S words but not C4 words. This result is in contrast to written verbal fluency performance in other degenerative motor disorders such as Amyotrophic Lateral Sclerosis (Abrahams *et al.*, 2000).

Verbal fluency indices (VFi and wVFI in the written task) were calculated to control for potential motor problems in the PD population making this measure a more accurate reflection of fluency task performance. In the spoken verbal fluency task, PD patients had significantly longer VFi's than controls in the total PRW index and all of the individual letter conditions. This result supports the word output analyses and suggests that the PD patients had a selective impairment in this task. In terms of the written verbal fluency

indices, PD patients showed the same pattern of results in the individual letter conditions; significantly longer wVFi's were found in the S condition but not the C4. This result does not support the executive dysfunction account of PD performance, as this account predicts worse performance in the C4 condition which is more executively demanding due to the restrictions placed on retrieval strategies (Abrahams *et al,* 2000). The slowed information-processing account postulates that patients would be impaired relative to controls in both letter conditions, and as such this account is not supported either. However, in contrast to the word output analyses, the significant difference in average wVFi across both letters indicated that the PD group were relatively impaired in this task. Furthermore, the result suggests that the VFi methodology is more sensitive to fluency deficits than total word output measures.

Clustering and switching analyses were employed in the spoken fluency task. The aim of these analyses was to dissociate automatic processing (clustering) from effortful executive processing (switching) (Troyer, Moscovitch & Winocur, 1997; Troyer *et al.,* 1998). Taking the comments of Mayr (2002) into consideration, the analyses were performed to reflect the amount of time that participants dedicated to clustering and switching components. Analysis of the average clustering and switching times across the PRW conditions revealed significant group differences suggesting that PD patients were slower than controls in both components. A significant effect of fluency component showed that both groups had longer switching times than clustering times indicating that the switching component was indeed more demanding. Analysis of the average PRW conditions did not show a significant interaction suggesting that PD performance, although relatively slower, essentially mirrored that of controls. At first glance this result would appear to support the slowed information-processing account which predicted slowed PD performance relative to controls in both fluency components. However, subsequent analyses of clustering and switching patterns in the individual letter conditions revealed different relationships.

In the P and R letter conditions, both groups performed comparatively; there was a main effect of fluency component showing that switching times were consistently longer than

clustering times, but no significant group differences. A look at the means in the letter conditions shows that group differences in clustering were small; moreover, PD patients actually displayed faster clustering times than controls in the R condition. In contrast to the other letter conditions, analysis of the W condition showed a significant interaction revealing that PD patients had disproportionately slower switching times than controls in this condition. This result showed that the PD group were impaired on the executive component of the most demanding letter condition suggesting the presence of a subtle executive dysfunction. The pattern of results in the individual letter conditions shows that the average PRW findings were misleading. The significant group difference was only driven by the interaction present in the W condition suggesting that in fact, PD patients were not impaired in the clustering components of any letter condition. However, it should be noted that the interaction in the W condition may have been a reflection of higher task demands rather a pure switching deficit (Azuma *et al.*, 1997). Never-the-less, the clustering and switching analyses are more supportive of the executive dysfunction account of PD performance as disproportionately slowed switching times were evident in one of the letter conditions.

The current study supports findings of Donovan *et al.* (1999) who reported that PD patients made less switches than controls. By contrast, the current investigation opposes earlier clustering and switching investigation such as Troster *et al.* (1998) which concluded that fluency performance in "completely normal" in non-demented PD patients. Troster *et al.* (1998) employed a different methodology to the current study in which analyses were made qualitatively rather than quantitatively; thus it would appear that the quantitative method is more sensitive to the fluency impairments present in PD. In addition the current study support the findings of Troyer, Moscovitch and Winocur (1997) in suggesting that the switching component of fluency tasks is more executively demanding and likely to mediated by the frontal lobes. Neuroimaging and neuropsychological studies have supported the role of the frontal lobes in phonemic fluency tasks (Abrahams *et al.*, 2003; Troyer *et al.*, 1998). Thus, evidence of disproportionately impaired switching in PD patients supports the postulated disruption of frontostriatal circuitry (Zgaljardic *et al.*, 2003; Owen, 2004).

Further experimental fluency measures were designed to examine verbal fluency performance under different levels of executive load. The syllabic fluency tasks required the same basic processes as verbal fluency tasks, with the addition of more stringent retrieval criteria imposed by the syllabic constraint. Furthermore, the task places high demands on attentional monitoring and inhibition to prevent the generation of words out with the constraints. PD patients were impaired relative to controls in 2 and 3 syllable manipulations of the task as indicated by the significant group difference; a relationship predicted by the slowed information-processing account. PD patients did not display the pattern of results predicted by the executive dysfunction account as performance in the 3 syllable condition (more executively demanding) was not disproportionately worse than that of controls. However, the group means show that PD patients performed at the same level in both syllable conditions, whereas the controls got worse as the syllabic constraints increased. This pattern of performance suggested that the PD group might have been performing at floor level, rather than mirroring the performance of controls at a relatively slower rate as predicted by the information processing account.

A comparison between the syllabic conditions and the P condition from the standard fluency task revealed that PD patients had disproportionately slower word generation times compared to controls on the 2 syllable fluency constraint (see Figure 7). This interaction suggested that PD patients were having marked difficulty with the heavy executive demands imposed by the syllabic constraint. The poor scores exhibited by PD patients in the syllabic conditions may be reflection of a failure to generate appropriate retrieval strategies. Normal clustering techniques are less likely to work in the syllabic fluency tasks as many related words will not conform to the specific syllabic constraint. Thus, poor performance in this task is not likely a reflection of slow clustering time. Rather, poor performance is likely to be a function of impaired functioning in the executive domains of strategic retrieval and response monitoring.

The final experimental paradigm aimed to directly investigate the affect of executive load on information-processing speed. Analyses of the NIP task produced a significant

interaction between group and executive load which suggested that the PD patients were disproportionately slower in the final NIP condition. Indeed, analyses of the individual task conditions revealed that there were no group differences in the NIP A (no executive load), and NIP B (low executive load) conditions suggesting that information-processing speed in PD patients was normal. However, a significant group difference was evident in the NIP C (high executive load) condition. This result is clear evidence that PD performance only differed from that of controls in tasks which imposed high executive demands. Thus, basic information processing speed appeared to be intact in the PD population whereas slowed performance that differentiated patients from controls could only be attributed to executive dysfunction. In addition, it would appear that this newly developed paradigm has the potential to be a sensitive measure of executive impairment in PD.

The performance exhibited by the PD group in the NIP task casts doubt on the findings of previous studies that postulated that impairments in fluency tasks are underpinned by slowed information-processing (e.g. Flowers, Robertson & Sheridan, 1995; Bittner & Crowe, 2007). The reported results also oppose those of Wilson *et al.* (1980) who found that PD thinking times increased significantly more than that of controls as the quantity of information to be scanned in working memory increased. The authors attributed this result to a deficit in information processing speed. However, in reality, increasing the load of working memory may be a reflection of executive functioning rather than information-processing, especially given the fact that working memory is acknowledged to be a crucial component of many executive processes (Baddeley & Della Sala, 1998).

Overall, the results of the current investigation support the hypothesis that a specific executive function is responsible for the patterns of impaired verbal fluency in PD. The PD cohort were impaired relative to controls in background measures of executive functioning, showed evidence of disproportionately slowed switching times in a verbal fluency condition, and performed significantly worse than controls in the syllabic fluency tasks. Moreover, PD patients displayed normal information-processing speeds that were subsequently disrupted in the condition that imposed high executive demands. There was

no evidence of general cognitive slowing (bradyphrenia) as PD patients were comparable to controls in some components of the experimental tasks, but showed significantly slowing in some of the more executive components. Thus, the pattern of performance exhibited by PD patients in the current investigation is best explained in terms of executive dysfunction. The impairments in verbal fluency are indicative of specific problems in the generation retrieval strategies, and the subsequent ability to switch between different strategies. The impairment in the final condition of the NIP task is more suggestive of an attentional deficit as a high amount of vigilance is required to monitor the processes required to make the numeric judgement.

Verbal fluency tasks rely on the ability to generate and monitor responses that cannot be aided by external environmental cues – hence they require intrinsic (internally generated) responses. The observed PD impairments are analogous to deficits in constructs such as Baddeley's (1996) "central executive" and Shallice's (1988) "SAS" which implement and control the allocation of attention and cognitive resources to achieve intrinsically driven behaviours. Disruption to either of these cognitive systems results in failures of initiation, planning, set-shifting and attentional monitoring, all of which are likely to have a detrimental effect on tasks such as verbal fluency. Patients were only disproportionately slowed in *one* verbal fluency condition (W), and in the *highest* executive load condition of the NIP task which suggests that the proposed executive deficit may be quite subtle. This may go some way to explaining the inconsistencies in the PD verbal fluency literature discussed earlier. The subtlety of the PD deficits may reflect a reduced attentional capacity (Revonsuo *et al.,* 1993). As such, tasks requiring relatively low attentional resources can be completed competently, but a dysfunction becomes evident when the attentional demands of a task exceed a threshold. However, it is also possible that executive deficits were affecting performance in the other tasks, but potential interactions were missed due to low study power.

The executive nature of the performance decrements observed in the PD group support the involvement of frontal lobe pathology in the disorder. Neuropsychological evidence has highlighted the involvement of DLPFC in mediating executive processing (Stuss &

Benson, 1986; Baddeley & Della Sala, 1998), and advancements in neurophysiology have provided physical evidence of frontal pathology in PD (Alexender, Crutcher & Delong, 1990). Frontostriatal circuits originate in the caudate nucleus (part of the striatum) and project to discrete areas of the frontal lobes. These connective structures, and in particular the dorsolateral prefrontal circuit, are affected by depleted dopamine levels within substantia nigra and the striatum (Owen, 2004). Frontostriatal pathology is likely to disrupt the flow of information between the basal ganglia and the target frontal regions, which may have a knock-on effect on cortical functioning. Thus, executive dysfunction in PD may be caused by the disruption of fronto-subcortical connections (Zgaljardic *et al.*, 2003). However, the connective nature of this pathology may suggest that information-processing speed also likely to be impaired in PD. If this is the case, it would seem likely that the slowing is specific to frontal regions and affects executive functions rather than causing a general slowing of all cognitive processes (bradyphrenia). In addition, the mesocortical pathway may contribute to the executive deficits observed in PD as it represents a direct, dopamine dependent link between the basal ganglia and frontal regions (Mattay *et al.*, 2002). The relative contributions of these pathways to PD cognitive pathology are highly pertinent to future investigations.

4.2 Limitations and future directions

There were several limitations associated with the current study that should be addressed in any future lines of investigation. The current study had a cohort of eight patients and eight controls, and whilst significant group differences were apparent through-out the investigation, the lack of statistical power may have caused potential interactions to be missed. In addition, small group sizes are very susceptible to the effect of outliers; relatively large changes in the means can be generated from a single wayward performance. Thus, future studies should attempt to recruit larger cohorts to increase statistical power and reliability. Also of note is the relatively high pre-morbid IQ's of the PD group – this may reflect greater interest in scientific research from individuals with a higher levels of education. Although the control group were well matched for intelligence, the study still did not reflect the demographics of the average population. It

is possible that high intelligence may mediate problems with cognitive functioning; therefore a more representative population is desirable.

Previous research has shown that PD is a very heterogeneous disorder (Graham & Sagar, 1999; Owen, 2004). If this is the case, then the possibility arises that patients of different subtypes could cancel each other out in terms of average group performance. Hence, it may be useful for future investigations to split patients into groups on the basis of neuropsychological tests of executive function before further experimental analysis. Another potential source of variability in PD performance arises from different dopamine treatments in individuals. As shown by Rowe *et al.* (2008), cortical areas mediating discrete functions require different dopamine levels for optimal performance, and these levels are affected by disease severity and medication. The current study did not control for individual medication levels or disease severity and as such there may have been a large amount of variation within the results.

In terms of the experimental methodology, two main caveats were identified. In the syllabic fluency task, it would have been useful to compare performance in a standard fluency task, such as the letter P (with any amount of syllables), to each of the syllabic conditions. This was not possible in the current investigation because the letters used in the standard task and in the syllabic task were not counterbalanced – therefore differences in performance could have been a reflection of relative letter difficulty (the letters M and F may be more difficult than P) rather than the syllabic constraint itself. Future investigations should counterbalance letters across conditions to avoid this problem. A possible caveat of the NIP methodology is derived from the requirement to perform mathematical estimations in the NIP C condition. This may provide a bias to participants with favourable baseline mathematical abilities. However, this occurrence seems unlikely given the basic nature of the mathematical component and the fact that the education level and pre-morbid IQ of both groups were relatively high. Despite these issues, the new measures employed in the current study showed good potential to dissociate PD patients from controls in terms of executive functioning. Therefore, future investigations should continue to refine and develop these methodologies.

4.3 Conclusion

PD patients were impaired in terms of their verbal fluency indices in all but one fluency measure, a result that showed the sensitivity of this measurement in populations with movement disorders. There was no evidence of slowed clustering in the PD group suggesting that within cluster retrieval was normal. However, PD switching was disproportionately slowed in the most demanding letter condition which may have reflected an executive dysfunction. The other experimental measures supported this finding as they indicated that PD patients were significantly impaired relative to controls in tasks which imposed high executive demands. Furthermore, PD patients performed normally in NIP conditions which required low cognitive loads showing that information-processing abilities were intact, and bradyphrenia was absent. The clustering and switching methodologies were not as sensitive to PD impairments as hoped, however this may have been a reflection of low statistical power. The newly developed measures employed by the study showed good potential in the identification of subtle executive deficits. In conclusion, the current study supported the hypothesis that verbal fluency deficits in PD reflect an underlying executive dysfunction. At present, disruptions in frontostriatal circuitry would seem the most likely neuropathological mechanism of the observed impairments.

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Appendices

Appendix A: Instructions for Spoken and Written Verbal Fluency Tests

Spoken Verbal Fluency (Abrahams et al., 2000)

'P' Generation Condition:

I am going to give you a letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people, places or numbers. So if I gave you the letter 'F' you would not say Frank, or Finland and no numbers. Try to avoid producing different endings of the same root word. So if I gave you the letter 'E' and you said 'eat', you wouldn't then say 'eating'. Any questions? Are you ready? You've got a minute and the letter is 'P'. "Start"

'P' Control Condition:

I am now going to ask you to read aloud the list you've just said. I have printed these words out. All you have to do is read this list in order. You must say all the 'P' words as fast as you can. Any questions? Are you ready? "Start"

'R' Generation Condition:

I am going to give you a different letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people, places or numbers. (Repeat the above example if necessary) Any questions? Are you ready? You've got a minute and the letter is 'R'. "Start"

'R' Control Condition:

Just like last time, I am now going to ask you to read aloud the list you've just said. I have printed these words out. All you have to do is read this list in order. You must say all the 'R' words as fast as you can. Any questions? Are you ready? "Start"

'W' Generation Condition:

I am going to give you another letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people, places or numbers. (Repeat the above example if necessary) Any questions? Are you ready? You've got a minute and the letter is 'W'. "Start"

‘W’ Control Condition

Just like last time, I am now going to ask you to read aloud the list you’ve just said. I have typed these words out. All you have to do is read this list in order. You must say all the ‘W’ words as fast as you can. Any questions? Are you ready? “Start”

Syllabic Verbal Fluency (the current study)

2 syllable condition:

I am going to give you a letter of the alphabet and I want you to generate as many words as you can beginning with that letter a minute. The words you generate must contain 2 syllables (no more, no less). The same rules apply as before; no names or numbers, and no different ending of the same root word. You’ve got 1 minute to generate as many words as possible. Any questions? Are you ready? “Start”

2 syllable control condition:

As before, I am now going to ask you to read aloud the list you’ve just said. I have typed these words out. All you have to do is read this list in order. You must say all the ‘W’ words as fast as you can. Any questions? Are you ready? “Start”

3 syllable condition:

I am going to give you a letter of the alphabet and I want you to generate as many words as you can beginning with that letter a minute. This time the words you generate must contain 3 syllables (no more, no less). The same rules apply as before; no names or numbers, and no different ending of the same root word. You’ve got 1 minute to generate as many words as possible. Any questions? Are you ready? “Start”

3 syllable control condition:

As before, I am now going to ask you to read aloud the list you’ve just said. I have typed these words out. All you have to do is read this list in order. You must say all the ‘W’ words as fast as you can. Any questions? Are you ready? “Start”

Written Verbal Fluency (Abrahams et al., 1996, 1997)

‘S’ Generation Condition:

I am going to give you a letter of the alphabet and I want you to write down as many words as you can beginning with that letter in 5 minutes. I do not want you to write any proper names (i.e. names of places or people). So if I gave you the letter ‘F’ you would

not write Frank, Finland and no numbers. Try to avoid producing different endings of the same root word. So if I gave you the letter ‘E’ and you wrote ‘eat’, you wouldn’t then write ‘eating’. You’ve got 5 minutes to generate as many words as you can beginning with the letter ‘S’. Any questions? Are you ready? “Start”

‘S’ Copy Condition:

I am now going to ask you to copy the list you’ve just written. All you have to do is write out this list again in order. You must copy all ‘S’ words as fast as you can. Any questions? Are you ready? “Start”

‘C’ Generation Condition:

I would now like you to write down as many 4 letter words (no more or less than 4 letters) beginning with ‘C’ that you can think of. Remember, I do not want names of people, places, numbers or variations of the same word (give the example above again if necessary. You have 4 minutes to write this list. Any questions? Are you ready? “Start”

‘C’ Copy Condition:

I am now going to ask you to copy the list you’ve just written. All you have to do is write out this list again in order. You must copy all ‘C’ words as fast as you can. Any questions? Are you ready? “Start”

Appendix B: Scoring Rules for Clustering and Switching Measures

Total number of correct words generated

This was the summation of all words generated minus all error types and repetitions. Eight error types were devised.

1. Nonsense words: words which were not found in the Oxford English Dictionary (2008). Spelling mistakes were treated leniently.
2. Proper nouns: names of people, places, days of the week, months of the year, brand names.
3. Repetitions
4. Abbreviations
5. Intrusions: the generation of a word beginning with a letter not asked for, for example, a 'H' word appearing in the 'S' generation list.
6. Numbers: the number itself (e.g. 7) or its written version (e.g. seven)
7. 'C' Words more than 4 letters
8. Derivatives: Words which formed another by derivation through the addition of a suffix, for example, "eat, eaten, eats, eating". In the case of the latter, a score of one (one correct, three errors) would be earned as all of these words share meaning. However, "elect, electron, electricity", would earn a score of three as all have separate meanings.

Cluster Types (loosely based on Troyer et al., 1997)

Semantic Clusters: groups of successively generated words which share a semantic attribute. There were 5 semantic cluster types considered:

1. Same Category: words which were derived from the same semantic category, for example, words pertaining to food such as "sausage, snack, seasoning and steamed".

2. Theme/Setting: words which relate to a shared theme, for example, a beach theme may be adopted and words such as “sand, sea surf, and shells” may be produced.
3. Different forms of the same word, for example, “sail and sale”.
4. Common phrases, literary verses, songs, such as “weeping, willow” and “ship, shape”.
5. Start with the same word: words are related in meaning such as “benefit, benefactor”.

Phonemic Clusters: groups of successively generated words that share a phonemic property attribute such as:

1. First Two Letters: words beginning with the same first two letters, such as “cart” and “camp”.
2. Rhyme: words that share the same last sounds, for example, “sweep” and “sleep”.
3. First and Last Sounds: words that share beginning and ending sounds and differ only by their vowel sounds, for example, “pant, punt, pint”.
4. Homonyms: words which are spelled or pronounced in the same way as another word, for example, “bank (financial institution) and bank (river edge).
5. Start with the Same Word: words which share the same beginning but are unrelated and have separate meanings, for example, “sentiment and sentinel”.

<u>Clusters not fulfilling Phonemic and Switching Criteria</u>

Overlapping Clusters: A cluster of words which all have similar attributes but it is not possible to establish where a switch or a change in subcategory occurs. For example, the following is an overlapping cluster: “supple, sum, supremacy, *sup*, sap, sip, sop”. The word “sup” is connected to either end of the cluster and therefore it is not possible to determine a change in strategy. The time taken to write ‘s’ of “supple” to the ‘p’ of “sop” was measured. Overlapping clusters were counted as one cluster.

A Cluster Within a Cluster: The following is an example of a cluster within a cluster: “stick, stuck, steal, stench”. “Stick” and “stuck” is a rhyming cluster, but all four words also form a phonetic cluster has they all share the same first two letters. A cluster within a cluster was counted as two clusters.

Single Word Clusters: Clusters comprising of one word only in which there was no occurrence of within cluster retrieval. Single word clusters were counted as zero.

* In order to establish cluster composition, errors and repetitions were included as these are thought to provide information about the underlying cognitive processes involved in this element of the task (Troyer et al., 1997).

Appendix C – Numerical Information Processing (NIP) task

NIP A: Identify the highest number

94 87 93 65 89	**13 37 51 36 75**
42 72 86 96 73	**91 88 82 30 25**
71 23 39 57 60	**49 27 43 98 77**
38 34 71 85 55	**50 83 64 63 86**
74 19 52 92 48	**46 81 66 79 27**
11 95 18 39 44	**80 84 27 17 15**
67 54 56 26 31	**16 35 53 61 90**
13 70 18 41 29	**14 78 46 22 62**
20 28 45 47 33	**21 12 59 97 15**
69 65 58 40 14	**95 31 24 22 16**
28 84 23 17 76	**53 42 63 35 68**
10 55 92 19 41	**82 73 26 18 54**
75 63 34 22 96	**66 39 75 70 50**
52 40 48 98 15	**49 85 51 87 64**
59 24 69 51 90	**71 81 72 93 56**

NIP A Motor Control: Mark the highlighted number

94 87 93 65 89	**13 37 51 36 75**
42 72 86 96 73	**91 88 82 30 25**
71 23 39 57 60	**49 27 43 98 77**
38 34 71 85 55	**50 83 64 63 86**
74 19 52 92 48	**46 81 66 79 27**
11 95 18 39 44	**80 84 27 17 15**
67 54 56 26 31	**16 35 53 61 90**
13 70 18 41 29	**14 78 46 22 62**
20 28 45 47 33	**21 12 59 97 15**
69 65 58 40 14	**95 31 24 22 16**
28 84 23 17 76	**53 42 63 35 68**
10 55 92 19 41	**82 73 26 18 54**
75 63 34 22 96	**66 39 75 70 50**
52 40 48 98 15	**49 85 51 87 64**
59 24 69 51 90	**71 81 72 93 56**

NIP B: Identify the second highest number

94 87 93 65 89	**13 37 51 36 75**
42 72 86 96 73	**91 88 82 30 25**
71 23 39 57 60	**49 27 43 98 77**
38 34 71 85 55	**50 83 64 63 86**
74 19 52 92 48	**46 81 66 79 27**
11 95 18 39 44	**80 84 27 17 15**
67 54 56 26 31	**16 35 53 61 90**
13 70 18 41 29	**14 78 46 22 62**
20 28 45 47 33	**21 12 59 97 15**
69 65 58 40 14	**95 31 24 22 16**
28 84 23 17 76	**53 42 63 35 68**
10 55 92 19 41	**82 73 26 18 54**
75 63 34 22 96	**66 39 75 70 50**
52 40 48 98 15	**49 85 51 87 64**
59 24 69 51 90	**71 81 72 93 56**

NIP B Motor Control: Mark the highlighted number

94 87 **93** 65 89	13 37 **51** 36 75
42 72 **86** 96 73	91 **88** 82 30 25
71 23 39 57 **60**	49 27 43 98 **77**
38 34 **71** 85 55	50 **83** 64 63 86
74 19 52 92 48	46 81 66 **79** 27
11 95 18 39 **44**	**80** 84 27 17 15
67 54 **56** 26 31	16 35 53 **61** 90
13 70 18 **41** 29	14 78 46 22 **62**
20 28 **45** 47 33	21 12 **59** 97 15
69 **65** 58 40 14	95 **31** 24 22 16
28 84 23 17 **76**	53 42 **63** 35 68
10 **55** 92 19 41	82 **73** 26 18 54
75 63 34 22 96	66 39 75 **70** 50
52 40 48 98 15	49 **85** 51 87 64
59 24 **69** 51 90	71 **81** 72 93 56

NIP C: Is the middle number higher or lower than the smallest number doubled?

					High	Low						High	Low
94	**87**	**<u>93</u>**	**65**	**89**	☐	☐	**13**	**37**	**<u>51</u>**	**36**	**75**	☐	☐
42	**72**	**<u>86</u>**	**96**	**73**	☐	☐	**91**	**88**	**<u>82</u>**	**30**	**25**	☐	☐
71	**23**	**<u>39</u>**	**57**	**60**	☐	☐	**49**	**27**	**<u>43</u>**	**98**	**77**	☐	☐
38	**34**	**<u>71</u>**	**85**	**55**	☐	☐	**50**	**83**	**<u>64</u>**	**63**	**86**	☐	☐
74	**19**	**<u>52</u>**	**92**	**48**	☐	☐	**46**	**81**	**<u>66</u>**	**79**	**27**	☐	☐

					High	Low						High	Low
11	**95**	**<u>18</u>**	**39**	**44**	☐	☐	**80**	**84**	**<u>27</u>**	**17**	**15**	☐	☐
67	**54**	**<u>56</u>**	**26**	**31**	☐	☐	**16**	**35**	**<u>53</u>**	**61**	**90**	☐	☐
13	**70**	**<u>18</u>**	**41**	**29**	☐	☐	**14**	**78**	**<u>46</u>**	**22**	**62**	☐	☐
20	**28**	**<u>45</u>**	**47**	**33**	☐	☐	**21**	**12**	**<u>59</u>**	**97**	**15**	☐	☐
69	**65**	**<u>58</u>**	**40**	**14**	☐	☐	**95**	**31**	**<u>24</u>**	**22**	**16**	☐	☐

					High	Low						High	Low
28	**84**	**<u>23</u>**	**17**	**76**	☐	☐	**53**	**42**	**<u>63</u>**	**35**	**68**	☐	☐
10	**55**	**<u>92</u>**	**19**	**41**	☐	☐	**82**	**73**	**<u>26</u>**	**18**	**54**	☐	☐
75	**63**	**<u>34</u>**	**22**	**96**	☐	☐	**66**	**39**	**<u>75</u>**	**70**	**50**	☐	☐
52	**40**	**<u>48</u>**	**98**	**15**	☐	☐	**49**	**85**	**<u>51</u>**	**87**	**64**	☐	☐
59	**24**	**<u>69</u>**	**51**	**90**	☐	☐	**71**	**81**	**<u>72</u>**	**93**	**56**	☐	☐

NIP C Motor Control: Mark the highlighted box

					High	Low						High	Low
94	87	**93**	65	89	☐	☐	13	37	**51**	36	75	☐	☐
42	72	**86**	96	73	☐	☐	91	88	**82**	30	25	☐	☐
71	23	**39**	57	60	☐	☐	49	27	**43**	98	77	☐	☐
38	34	**71**	85	55	☐	☐	50	83	**64**	63	86	☐	☐
74	19	**52**	92	48	☐	☐	46	81	**66**	79	27	☐	☐

					High	Low						High	Low
11	95	**18**	39	44	☐	☐	80	84	**27**	17	15	☐	☐
67	54	**56**	26	31	☐	☐	16	35	**53**	61	90	☐	☐
13	70	**18**	41	29	☐	☐	14	78	**46**	22	62	☐	☐
20	28	**45**	47	33	☐	☐	21	12	**59**	97	15	☐	☐
69	65	**58**	40	14	☐	☐	95	31	**24**	22	16	☐	☐

					High	Low						High	Low
28	84	**23**	17	76	☐	☐	53	42	**63**	35	68	☐	☐
10	55	**92**	19	41	☐	☐	82	73	**26**	18	54	☐	☐
75	63	**34**	22	96	☐	☐	66	39	**75**	70	50	☐	☐
52	40	**48**	98	15	☐	☐	49	85	**51**	87	64	☐	☐
59	24	**69**	51	90	☐	☐	71	81	**72**	93	56	☐	☐

Appendix D – Group means for verbal fluency errors and perseverations

Spoken Verbal Fluency

Fluency Condition	PD Patients		Controls	
	Errors	Perseverations	Errors	Perseverations
P	0.625	0.5	0.375	0.125
R	0.375	0.25	0.75	0.5
W	0.75	0.75	0.875	0.625

Written Verbal Fluency

Fluency Condition	PD Patients		Controls	
	Errors	Perseverations	Errors	Perseverations
S	1.57	1.29	1.75	0.125
C4	1.14	0.86	2.25	0.125

Appendix E – Group means for task errors in NIP conditions

Numerical Information Processing (NIP) task

NIP Condition	PD Patients	Controls
NIP A	0.875	0.375
NIP B	1.375	1.875
NIP C	1.875	0.75

Appendix F- Hoehn and Yahr Staging of Parkinson's disease (1967).

Stages:

0: No visible symptoms of Parkinson disease.

1: Symptoms confined to one side of the body, e.g. tremor of one limb.

2: Symptoms on both sides of the body. No difficulty walking.

3: Symptoms on both sides of the body. Minimal difficulty with walking and balance (short stride, shuffle).

4; Disabling symptoms on both sides of the body. Moderate difficulty walking.

5: Severely disabling symptoms on both sides of the body. Unable to walk.